

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA**

HUMAN GENOME SCIENCES, INC.
14200 Shady Grove Road
Rockville, MD 20850

Plaintiff,

v.

Case No.: _____

DAVID J. KAPPOS, in his official capacity as
Under Secretary of Commerce for Intellectual
Property and Director of the United States Patent
and Trademark Office

Office of the General Counsel
United States Patent and Trademark Office
P.O. Box 15667, Arlington, VA 22215

Defendant.

COMPLAINT

Plaintiff Human Genome Sciences, Inc. ("HGS"), for its complaint against the Honorable David J. Kappos, states as follows:

NATURE OF THE ACTION

1. This is an action by the assignee of United States Patent Nos. 7,601,351 ("the '351 patent") and 7,605,236 ("the '236 patent") seeking judgment, pursuant to 35 U.S.C. § 154(b)(4)(A), that the patent term adjustment for the '351 patent be changed from 983 days to 1546 days, or at least 1,542 days and the patent term adjustment for the '236 patent be changed from 209 days to 478 days, or at least 416 days.

JURISDICTION AND VENUE

2. This action arises under 35 U.S.C. § 154 and the Administrative Procedure Act, 5 U.S.C. §§ 701-706.

3. This Court has jurisdiction to hear this action and is authorized to issue the relief sought pursuant to 28 U.S.C. §§ 1331, 1338(a), and 1361, 35 U.S.C. § 154(b)(4)(A), and 5 U.S.C. §§ 701-706.

4. Venue is proper in this district by virtue of 35 U.S.C. § 154(b)(4)(A).

5. This Complaint is being timely filed in accordance with 35 U.S.C. § 154(b)(4)(A) and Fed. R. Civ. P. 6(a)(3).

THE PARTIES

6. Plaintiff HGS is a corporation, organized, existing and doing business under and by virtue of the laws of the State of Delaware, with its principal place of business located at 14200 Shady Grove Road, Rockville, MD 20850.

7. Defendant David Kappos is sued in his official capacity as Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office ("PTO"). The Director of the PTO is designated by statute as the official responsible for determining the period of patent term adjustments, and thus is the proper defendant in a suit seeking review of such determinations. *See* 35 U.S.C. §§ 154(b)(3) and 154(b)(4)(A).

BACKGROUND

8. Section 154 of title 35 of the United States Code requires that the Director of the PTO grant a patent term adjustment ("PTA") in accordance with the provisions of section 154(b).

9. In determining patent term adjustment ("PTA"), the Defendant must take into account PTO delays under 35 U.S.C. § 154(b)(1), any overlap in PTO delays under 35 U.S.C. § 154(b)(2)(A), and any "Applicant delay" under 35 U.S.C. § 154(b)(2)(C).

10. PTO delays under 35 U.S.C. § 154(b)(1) break down into three categories known as "A delay," "B delay," and "C delay." Only "A delay" and "B delay" are at issue in this case.

11. "A delay" occurs when the PTO fails to act within a particular time period; for example, if the PTO does not "issue a patent within four months after the date on which the issue fee was paid . . . and all other outstanding requirements were satisfied." *See* 35 U.S.C. § 154(b)(1)(A). The statute provides that "the term of the patent shall be extended by 1 day for each day after the end of the period specified . . . until the action described . . . is taken." *Id.*

12. "B delay" occurs when the PTO fails to issue a patent within three years of the actual filing date of the patent application, excluding certain periods of delay attributable to the applicant. *See* 35 U.S.C. § 154(b)(1)(B). Similarly to "A delays," the statute provides that "[T]he term of the patent shall be extended by 1 day for each day after the end of that 3-year period until the patent is issued." *Id.*

13. 35 U.S.C. § 154(b)(3)(B) states that "the Director shall- (i) make a determination of the period of any patent term adjustment under this subsection, and shall transmit a notice of that determination with the written notice of allowance of the application"

14. The PTO had taken the position that whenever an application is subject to both “A delay” and “B delay,” those periods always “overlap” within the meaning of 35 U.S.C. § 154(b)(2)(A) even if they occur on different calendar days. Thus, for the purposes of PTA, the PTO counted the greater of the “A delay” or the “B delay,” but never both periods of delay.

15. This Court rejected the PTO’s interpretation of 35 U.S.C. § 154(b)(2)(A) in *Wyeth v. Dudas*, 580 F. Supp. 2d 138 (D.D.C. 2008), and this holding was affirmed by the Federal Circuit in *Wyeth v. Kappos*, 591 F.3d 1364 (Fed. Cir. 2010). The Court held that “[t]he only way that periods of time can ‘overlap’ is if they occur on the same day” under 35 U.S.C. § 154(b)(2). *Id.* at 141. Thus, “[i]f an ‘A delay’ occurs on one calendar day and a ‘B delay’ occurs on another, they do not overlap, and § 154(b)(2)(A) does not limit the extension to one day.” *Id.* at 141-42.

16. “Applicant delay” under 35 U.S.C. § 154(b)(2)(C) arises where an applicant “failed to engage in reasonable efforts to conclude prosecution of the application,” and results in a reduction of any accumulated PTA. *See* 37 C.F.R. § 1.704(a). The Director has prescribed regulations setting out the specific circumstances deemed to be “Applicant delay.” *See* 37 C.F.R. § 1.704.

17. At issue here is “Applicant delay” arising under 37 C.F.R. §§ 1.704(b), 1.704(c)(7) and 1.704(c)(8). Under 37 C.F.R. § 1.704(b), failure to reply within three months to “any notice or action by the Office making any rejection, objection, argument, or other request,” results in a reduction of PTA “by the number of days, if any, beginning on the day after the date that is three months after the date of mailing or transmission of the office communication notifying the applicant of the rejection, objection, argument or other request and ending on the date the reply was filed.”

18. Under 37 C.F.R. § 1.704(c)(8), “[s]ubmission of a supplemental reply or other paper, other than a supplemental reply or other paper expressly requested by the examiner, after a reply has been filed” constitutes “Applicant delay.” Delay under 37 C.F.R. § 1.704(c)(8) reduces PTA by “the number of days beginning on the day after the date the initial reply was filed and ending on the date that the supplemental reply or other such paper was filed.” Similarly, under 37 C.F.R. § 1.704(c)(7), “[s]ubmission of a reply having an omission ([37 C.F.R.] § 1.135(c))” constitutes “Applicant delay” and reduces PTA “by the number of days, if any, beginning on the day after the date the reply having an omission was filed and ending on the date that the reply or other paper correcting the omission was filed.”

19. Under 35 U.S.C. § 154(b)(4)(A), “[a]n applicant dissatisfied with a determination made by the Director under paragraph (3) shall have remedy by a civil action against the Director filed in the United States District Court for the District of Columbia within 180 days after the grant of the patent. Chapter 7 of title 5 shall apply to such action.”

The '351 Patent

20. Craig A. Rosen, Michael W. Laird, and Reiner L. Gentz are the inventors of the '351 patent, entitled “Antibodies Against Protective Antigen,” which issued from U.S. Patent Application No. 10/602,727 (“the '727 application”) on October 13, 2009. The '351 patent is attached hereto as Exhibit A.

21. HGS is the assignee of the '351 patent, as evidenced by the assignment documents recorded at the PTO.

22. The '351 patent was filed on June 25, 2003, and is thus eligible for PTA under 35 U.S.C. § 154.

23. The '351 patent is not subject to a terminal disclaimer.

24. The PTO failed to act on the '727 application within 14 months of the actual filing date. Thus, Plaintiff is entitled to 559 days of "A delay" due to the PTO's delay from the day after the date fourteen months after the application was filed (August 26, 2004) to the date of mailing of the first notification under 35 U.S.C. § 132 (March 7, 2006). *See* 35 U.S.C. § 154(b)(1)(A)(i) and 37 C.F.R. §§ 1.702(a)(1) & 1.703(a)(1).

25. A complete reply to the March 7, 2006 office action was filed on July 7, 2006 with a petition for an extension of time of three months. Pursuant to 37 C.F.R. § 1.704, this filing incurred a PTA reduction of 30 days from the day after the date three months after the mailing date of the office action (June 8, 2006) to the date of the response (July 7, 2006).

26. An information disclosure statement ("IDS") was filed on July 11, 2006. According to the Defendant, PTA was reduced by 4 days as a result of this filing. *See* Exhibit C, Dismissal of Application for Patent Term Adjustment, at 2-3. This reduction in PTA is in error because the reply filed July 7, 2006 was a complete reply under 35 U.S.C. § 132 in compliance with 35 U.S.C. § 154(b)(1)(A)(ii) and 37 C.F.R. §§ 1.702(a)(2) and 1.703(a)(2) to the office action of March 7, 2006. Thus, the IDS was not a "supplemental reply or other paper" under 37 C.F.R. § 1.704(c)(8).

27. Additionally, the PTO did not provide the July 7, 2006 filing to the responsible patent examiner until July 11, 2006, the same day as the July 11, 2006 IDS was filed. Thus, the IDS filing could not have delayed the patent examiner's consideration of Plaintiff's reply or the preparation of a response under 35 U.S.C. § 132. Accordingly, the submission of the IDS on July 11, 2006 cannot constitute a failure to "engage in reasonable efforts to conclude prosecution."

28. A Notice to Comply requesting a new Sequence Listing was mailed on October 13, 2006. The Notice to Comply to the Sequence Listing was incorrectly treated as a proper response to Plaintiff's reply of July 7, 2006. *See* Exhibit C, Dismissal of Application for Patent Term Adjustment, at 3-4. According to the Defendant, the period of adjustment was erroneously calculated as a 64-day adjustment, instead of a 254-day adjustment for the reasons discussed below. A response to the Notice to Comply was filed on January 16, 2007 with a petition for extension of time of two months. Pursuant to 37 C.F.R. § 1.704, this filing incurred a PTA reduction of 3 days from the day after the date that was three months after the mailing of the notice (January 14, 2007) to the date of the response (January 16, 2007).

29. A non-final office action responsive to Plaintiff's July 7, 2006 reply was mailed on July 19, 2007. Accordingly, Plaintiff is entitled to 254 days of "A delay" due to the PTO's delay in responding from the day after the date that is four months after the reply was filed (November 8, 2006) and ending on the date of mailing of the non-final office action under 35 U.S.C. § 132 (July 19, 2007). *See* 37 C.F.R. §§ 1.702(a)(2) and 1.703(a)(2).

30. A response to the July 19, 2007 non-final office action was filed on January 22, 2008 with a petition for an extension of time of three months. Pursuant to 37 C.F.R. § 1.704, this filing incurred a PTA reduction of 95 days from the day after the date that was three months after the mailing of the office action (October 20, 2007) to the date of the response (January 22, 2008).

31. A final office action was mailed on April 28, 2008. A response to the final office action was filed on October 27, 2008 with a petition for an extension of time of three months. Pursuant to 37 C.F.R. § 1.704, this filing incurred a PTA reduction of 91 days from the day after the date that was three months after the mailing of the office action (July 29, 2008) to the date of the response (October 27, 2008).

32. On December 10, 2008, a Notice of Allowance was mailed together with a determination of patent term adjustment of 400 days.

33. The issue fee transmittal form was filed and the issue fee was timely paid on March 6, 2009.

34. An Application for Patent Term Adjustment under 37 C.F.R. § 1.705(b) was timely filed on March 6, 2009. On September 14, 2009, Defendant mailed a decision indicating that the Application for Patent Term Adjustment was dismissed.

35. The Defendant, in its dismissal of Plaintiff's Application for Patent Term Adjustment stated that Plaintiff's July 7, 2006 reply to the office action constituted a reply having an omission under 37 C.F.R. § 1.704(c)(7). *See* Exhibit C, at 3. Plaintiff believes this determination to be incorrect; however, in the event this Court agrees with the Defendant, Plaintiff would still be entitled to 64 days of "A delay" from the day after four months from the date the Plaintiff filed its response to the Notice to Comply (May 17, 2007) until the date of mailing of the non-final office action under 35 U.S.C. § 132 (July 19, 2007). *Id.* at 4. Furthermore, Defendant stated that the IDS filed on July 11, 2006 constituted "Applicant delay" under 37 C.F.R. § 1.704(c)(8). *Id.* at 2-3. Plaintiff believes this determination is also incorrect; however, in the event this Court agrees with Defendant, Plaintiff would incur an additional reduction of PTA of 4 days from the date the Plaintiff filed its reply (July 7, 2006) until the date the IDS was filed (July 11, 2006).

36. The '351 patent issued on October 13, 2009; thus, the PTO failed to issue the '351 patent within four months of the payment of the issue fee pursuant to 35 U.S.C. § 154(b)(1)(A)(iv). Thus, Plaintiff is entitled to 99 days of "A delay" due to the PTO's delay from the day after the date four months after the issue fee was paid (March 7, 2009) to the date

of issuance of the '351 patent (October 13, 2009). *See* 35 U.S.C. § 154(b)(1)(A)(iv) and 37 C.F.R. §§ 1.702(a)(4) & 1.703(a)(6).

37. Furthermore, the PTO failed to issue the '351 patent within three years of its actual filing date pursuant to 35 U.S.C. § 154(b)(1)(B). Thus, Plaintiff is entitled to 1,206 days of "B delay" due to the PTO's failure to issue the patent from the day after the date that was three years after the application was filed (June 26, 2006) to the date that the patent was issued (October 13, 2009). *See* 35 U.S.C. § 154(b)(1)(B) and 37 C.F.R. § 1.703(b).

38. Accordingly, "A delay" under 35 U.S.C. § 154(b)(1)(A) amounted to 912 days ($559 + 254 + 99$), or alternatively 722 days ($559 + 64 + 99$) if the Defendant's determination is accepted. "B delay" under 35 U.S.C. § 154(b)(1)(B) amounted to 1,206 days. There were 353 days of overlap between the "A delay" and "B delay." Thus total PTO delay amounted to 1,765 days ($559 + 1,206$). Total "Applicant delay" amounted to 219 days, or at least no more than 223 days if the Defendant's determination is accepted. Thus, the total correct PTA for the '351 patent is 1,546 days, or at least 1,542 days.

39. On November 13, 2009, Plaintiff timely filed a Request for Reconsideration of Decision on Application for Patent Term Adjustment Under 37 C.F.R. § 1.705(b) and Application for Patent Term Adjustment Under 37 C.F.R. § 1.705(d). The request demonstrated that the correct PTA for the '351 patent is 1,546 days, or at least 1,542 days, rather than 983 days as currently calculated. The PTO has not yet issued a decision on this Petition.

40. The PTO's determination of the patent term adjustment for the '351 patent was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law under 5 U.S.C. § 706(2)(A).

The '236 Patent

41. Steven M. Ruben, Steven C. Barash, Gil H. Choi, Tristan Vaughan, and David Hilbert are the inventors of the '236 patent, entitled "Antibodies that Immunospecifically Bind to B Lymphocyte Stimulator Protein," which issued from U.S. Patent Application No. 11/266,444 ("the '444 application") on October 20, 2009. The '236 patent is attached hereto as Exhibit B.

42. HGS is the assignee of the '236 patent, as evidenced by the assignment documents recorded in the PTO.

43. The '236 patent was filed on November 4, 2005, and is thus eligible for PTA under 35 U.S.C. § 154.

44. The '236 patent is not subject to a terminal disclaimer.

45. The PTO failed to act on the '444 application within 14 months of the actual filing date. Plaintiff is thus entitled to "A delay" of 110 days due to the PTO's delay from the day after the date fourteen months after the application was filed (January 5, 2007) to the date of mailing of the first notification under 35 U.S.C. § 132 (April 24, 2007). *See* 35 U.S.C. § 154(b)(1)(A)(i) and 37 C.F.R. §§ 1.702(a)(1) and 1.703(a)(1).

46. A complete reply to the April 24, 2007 office action was filed on July 23, 2007 with a petition for an extension of time of two months. The complete reply was filed within three months after the mailing of the office action (April 24, 2007), thereby incurring no reduction in PTA under 37 C.F.R. § 1.704.

47. An IDS was filed on September 10, 2007. According to the Defendant, PTA was reduced by 49 days as a result of this filing. *See* Exhibit D, Dismissal of Application for Patent Term Adjustment, at 1-2. Pursuant to 37 C.F.R. § 1.97(b)(3), an IDS filed before the mailing of a first Office Action on the merits shall be considered by the Office. Thus, this reduction in PTA

is in error because the filing of the IDS prior to the first office action in accordance with PTO rules does not constitute a failure of Applicants to engage in reasonable efforts to conclude examination of the application under 37 C.F.R. § 1.704(c).

48. A non-final office action was mailed on February 28, 2008. However, the PTO failed to respond under 35 U.S.C. § 154(b)(1)(A)(ii) within the four month permitted time frame after Plaintiff's July 23, 2007 reply. Accordingly, Plaintiff is entitled to "A delay" of 97 days due to the PTO's delay from the day after the date four months after the reply was filed (November 24, 2007) until the date of mailing of the non-final office action under 35 U.S.C. § 132 (February 28, 2008). *See* 37 C.F.R. §§ 1.702(a)(2) & 1.703(a)(2).

49. A response to the February 28, 2008 non-final office action was filed on June 30, 2008 with a petition for an extension of time of one month. Pursuant to 37 C.F.R. § 1.704, this filing incurred a PTA reduction of 33 days from the day after the date three months after the mailing of the office action (May 29, 2008) to the date of the response (June 30, 2008).

50. A notice of informal or non-responsive amendment was mailed on August 4, 2008. A response to the August 4, 2008 notice of informal or non-responsive amendment was filed on August 15, 2008. Pursuant to 37 C.F.R. § 1.704, this filing incurred a PTA reduction of 46 days from the day after the date three months after the mailing of the office action (May 29, 2008) to the date of the response (August 15, 2008).

51. An IDS was filed on August 28, 2008. According to the Defendant, PTA was reduced by 13 days as a result of this filing. *See* Exhibit D, Dismissal of Application for Patent Term Adjustment, at 3. However, this reduction in PTA is in error because the reply filed August 15, 2008 was a complete reply under 35 U.S.C. § 132 in compliance with 35 U.S.C. § 154(b)(1)(A)(ii) and 37 C.F.R. §§ 1.702(a)(2) and 1.703(a)(2) to the office action of February 28,

2008. Thus, the IDS was not a “supplemental reply or other paper” under 37 C.F.R. § 1.704(c)(8).

52. Additionally, the PTO did not forward Plaintiff’s August 15, 2008 filing to the responsible patent examiner until September 19, 2008, more than one month after the August 28, 2008 IDS was filed. Thus, the IDS filing could not have delayed the patent examiner’s consideration of Plaintiff’s filing or the preparation of a response under 35 U.S.C. § 132, and thus the submission of the IDS on August 28, 2008 cannot constitute a failure to “engage in reasonable efforts to conclude prosecution.”

53. On April 2, 2009, a Notice of Allowance was mailed together with a Determination of Patent Term Adjustment under 35 U.S.C. § 154 indicating a PTA of 66 days.

54. The issue fee transmittal form was filed and the issue fee was timely paid, on July 2, 2009.

55. An Application for Patent Term Adjustment was timely filed on July 2, 2009. On September 16, 2009, the PTO mailed a decision indicating that the Application for Patent Term Adjustment was dismissed.

56. The ’236 patent issued on October 20, 2009. Thus, the PTO failed to issue the patent within three years pursuant to 35 U.S.C. § 154(b)(1)(B). As a result, Plaintiff is entitled to 350 days of “B delay” due to the PTO’s delay in issuing the patent from the day after the date that was three years after the application was filed (November 5, 2008) to the date that the patent was issued (October 20, 2009). *See* 35 U.S.C. § 154(b)(1)(B) and 37 C.F.R. § 1.703(b).

57. In sum, “A delay” under 35 U.S.C. § 154(b)(1)(A) amounted to 207 days. “B delay” under 35 U.S.C. § 154(b)(1)(B) amounted to 350 days. There were 0 days of overlap between the “A delay” and the “B delay.” Thus, total PTO delay amounted to 557 days (350 +

207). Total Applicant delay amounted to 79 days or, if the Defendant's determination is accepted, at least no more than 141 days. Thus, the total PTA for the '236 patent is 478 days, or at least 416 days if the Defendant's determination is accepted.

58. On November 16, 2009, Plaintiff filed a timely Request for Reconsideration of Decision on Application for Patent Term Adjustment Under 37 C.F.R. § 1.705(b) and Application for Patent Term Adjustment Under 37 C.F.R. § 1.705(d). The request demonstrated that the correct PTA for the '236 patent is 478 days, or at least 416 days, rather than 209 days as currently calculated. The PTO has not yet issued a decision on this petition.

59. The PTO's determination of the patent term adjustment for the '351 patent was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law under 5 U.S.C. § 706(2)(A).

CLAIM FOR RELIEF

60. The allegations of paragraphs 1-59 are incorporated in this claim for relief as if fully set forth herein.

The '351 patent

61. The patent term adjustment for the '351 patent, as determined by the Defendant under 35 U.S.C. § 154(b) and listed on the face of the '351 patent, is 983 days. See Exhibit A at 1.

62. Under 35 U.S.C. § 154(b)(1)(A), Plaintiff is entitled to an adjustment of the term of the '351 patent of 912 days, the number of days attributable to PTO examination delay ("A Delay").

63. Under 35 U.S.C. § 154(b)(1)(B), Plaintiff is entitled to an additional adjustment of the term of the '351 patent of a period of 1,206 days, which is the number of days the issue date of the '351 patent exceeded three years (from June 26, 2006 until October 13, 2009) ("B Delay").

64. 35 U.S.C. § 154(b)(2)(A) provides that "to the extent that periods of delay attributable to grounds specified in paragraph [b](1) overlap, the period of any adjustment . . . shall not exceed the actual number of days the issuance of the patent was delayed." In *Wyeth v. Dudas*, 580 F. Supp. 2d 138 (D.D.C. 2008), this Court explained that for purposes of identifying "overlap" between "A Delay" and "B Delay" under 35 U.S.C. § 154(b)(2)(A), the "period of delay" for "B Delay" begins when the PTO has failed to issue a patent within three years, not before.

65. In accordance with *Wyeth*, the correct patent term adjustment under 35 U.S.C. § 154(b)(1) and (2) is the sum of the "A Delay" and "B Delay" ($912 + 1,206 = 2,118$ days)

reduced by the number of days of “A Delay” that overlaps with “B Delay” (353 days) and reduced by the number of days of applicant delay (219 days, or at least not more than 223 days) for a net adjustment of 1,546 days, or at least not less than 1,542 days.

66. The Director erred in the determination of patent term adjustment by treating the filing of an IDS as a supplemental reply or other paper under 37 C.F.R. § 1.704(c)(8), and in holding that the filing of the IDS constituted a failure to engage in reasonable efforts to conclude prosecution under the circumstances. Thus, the Director erroneously determined that the Applicant delay amounted to 223 days, rather than the correct number of 219 days.

67. The Director erred in the determination of patent term adjustment by treating the “period of delay” for “B Delay” for purposes of identifying “overlap” under 35 U.S.C. § 154(b)(2)(A), as running from the filing date of the patent application rather than beginning when the PTO has failed to issue a patent within three years. Thus, the Director erroneously determined that all of the “A Delay” overlapped with the “B Delay” under 35 U.S.C. § 154(b)(2)(A), whereas the “A delay” and “B delay” only overlapped for 353 calendar days.

68. The Director’s determination that the ‘351 patent is entitled to only 983 days of patent term adjustment is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with the law and in excess of statutory jurisdiction, authority, or limitation.

The ‘236 patent

69. The patent term adjustment for the ‘236 patent, as determined by the Defendant under 35 U.S.C. § 154(b) and listed on the face of the ‘236 patent, is 209 days. *See* Exhibit B at 1.

70. Under 35 U.S.C. § 154(b)(1)(A), Plaintiff is entitled to an adjustment of the term of the '236 patent of 207 days, the number of days attributable to PTO examination delay ("A Delay") as calculated by the PTO.

71. Under 35 U.S.C. § 154(b)(1)(B), Plaintiff is entitled to an additional adjustment of the term of the '236 patent of a period of 350 days, which is the number of days the issue date of the '236 patent exceeded three years (from November 5, 2008 until October 20, 2009) ("B Delay").

72. 35 U.S.C. § 154(b)(2)(A) provides that "to the extent that periods of delay attributable to grounds specified in paragraph [b](1) overlap, the period of any adjustment . . . shall not exceed the actual number of days the issuance of the patent was delayed." In *Wyeth v. Dudas*, 580 F. Supp. 2d 138, 141 (D.D.C. 2008) this Court explained that for purposes of identifying "overlap" between "A Delay" and "B Delay" under 35 U.S.C. § 154(b)(2)(A), the "period of delay" for "B Delay" begins when the PTO has failed to issue a patent within three years, not before.

73. In accordance with *Wyeth*, the correct patent term adjustment under 35 U.S.C. § 154(b)(1) and (2) is the sum of the "A Delay" and "B Delay" (557 days) reduced by the number of days of "A Delay" that overlaps with "B Delay" (0 days) and reduced by the number of days of Applicant delay (79 days, or at least not more than 141 days) for a net adjustment of 478 days, or at least not less than 416 days.

74. The Director erred in the determination of patent term adjustment by treating the filing of two IDS submissions as "Applicant delay" under 37 C.F.R. § 1.704(c)(8), and in holding that the filing of the IDS submissions constituted failures to engage in reasonable efforts

to conclude prosecution under the circumstances. Thus, the Director erroneously determined that the Applicant delay amounted to 141 days, rather than the correct number of 79 days.

75. The Director erred in the determination of patent term adjustment by treating the "period of delay" for "B Delay" for purposes of identifying "overlap" under 35 U.S.C. § 154(b)(2)(A), as running from the filing date of the patent application rather than beginning when the PTO has failed to issue a patent within three years. Thus, the Director erroneously determined that all of the "A Delay" overlapped with the "B Delay" under 35 U.S.C. § 154(b)(2)(A), whereas the "A delay" and "B delay" did not overlap on any calendar day.

76. The Director's determination that the '236 patent is entitled to only 209 days of patent term adjustment is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with the law and in excess of statutory jurisdiction, authority, or limitation.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff demands judgment against Defendant and respectfully requests that this Court enter Orders:

A. Changing the period of patent term adjustment for the '351 patent from 983 days to 1,546 days, or at least 1,542 days, and requiring Defendant to extend the term of the '351 patent to reflect the 1,546 day, or at least 1,542 day, patent term adjustment;

B. Changing the period of patent term adjustment for the '236 patent from 209 days to 478 days, or at least 416 days, and requiring Defendant to extend the term of the '236 patent to reflect the 478 day, or at least 416 day, patent term adjustment; and

C. Granting such other and further relief as the nature of the case may admit or require and as may be just and equitable.

Respectfully submitted,

Dated: April 9, 2010

By: 

Jeremy M. Jay (D.C. Bar No. 427812)
LEYDIG, VOIT & MAYER, PC
700 Thirteenth Street, N.W., Suite 300
Washington, D.C. 20005-3960
Tel: (202) 737-6770
Fax: (202) 737-6776
E-mail: jjay@leydig.com

*Attorney for Plaintiff
Human Genome Sciences, Inc.*

EXHIBIT A



US007601351B1

(12) **United States Patent**
Rosen et al.(10) Patent No.: **US 7,601,351 B1**
(45) Date of Patent: **Oct. 13, 2009**

- (54) **ANTIBODIES AGAINST PROTECTIVE ANTIGEN**
- (75) Inventors: **Craig A. Rosen**, Laytonsville, MD (US);
Michael W. Laird, Germantown, MD (US); **Reiner L. Gentz**, Belo Horizonte-Mg (BR)
- (73) Assignee: **Human Genome Sciences, Inc.**, Rockville, MD (US)
- (*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 983 days.
- (21) Appl. No.: 10/602,727
- (22) Filed: Jun. 25, 2003

Related U.S. Application Data

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- (58) Field of Classification Search None
See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to antibodies and related molecules that specifically bind to protective antigen of *Bacillus anthracis* (PA). Such antibodies have uses, for example, in the prevention and treatment of anthrax and anthrax toxin poisoning. The invention also relates to nucleic acid molecules encoding anti-PA antibodies, vectors and host cells containing these nucleic acids, and methods for producing the same.

69 Claims, 7 Drawing Sheets

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Figure 1: Inhibition of PA-ATR binding

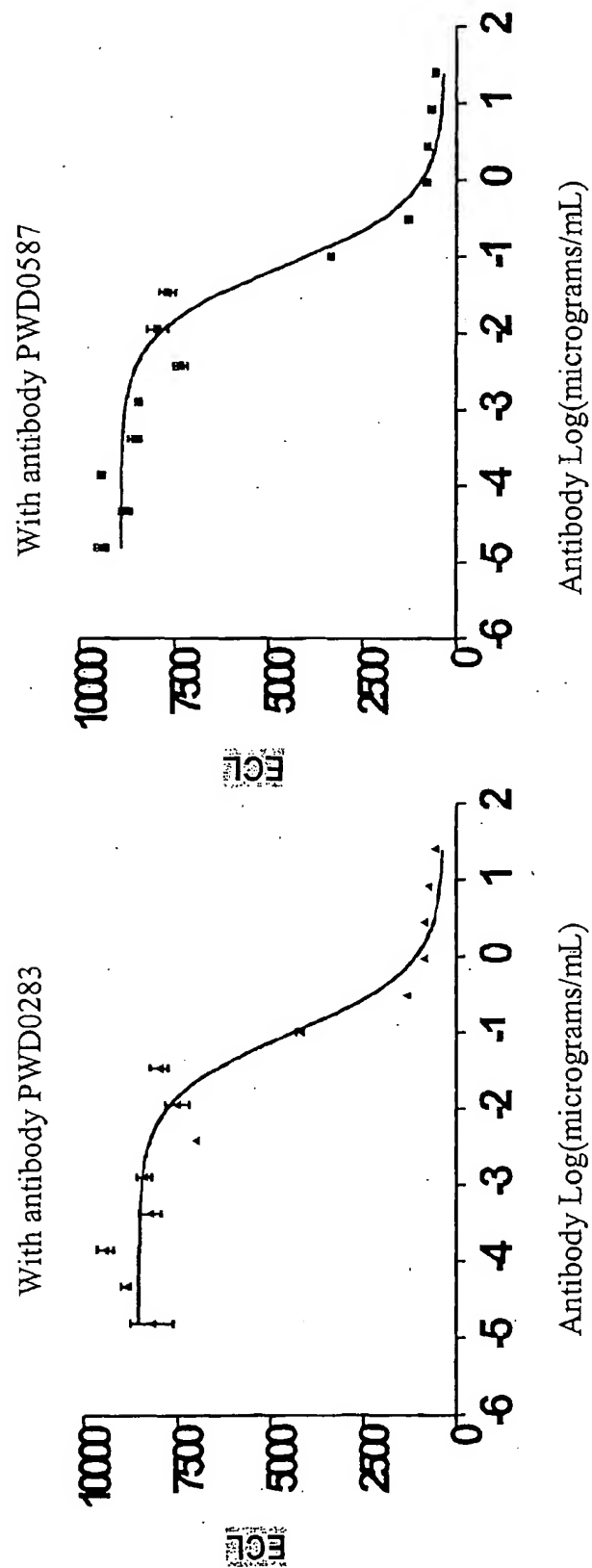


Figure 2: Binding of Biotinylated PA to Cells as Determined by Flow Cytometry

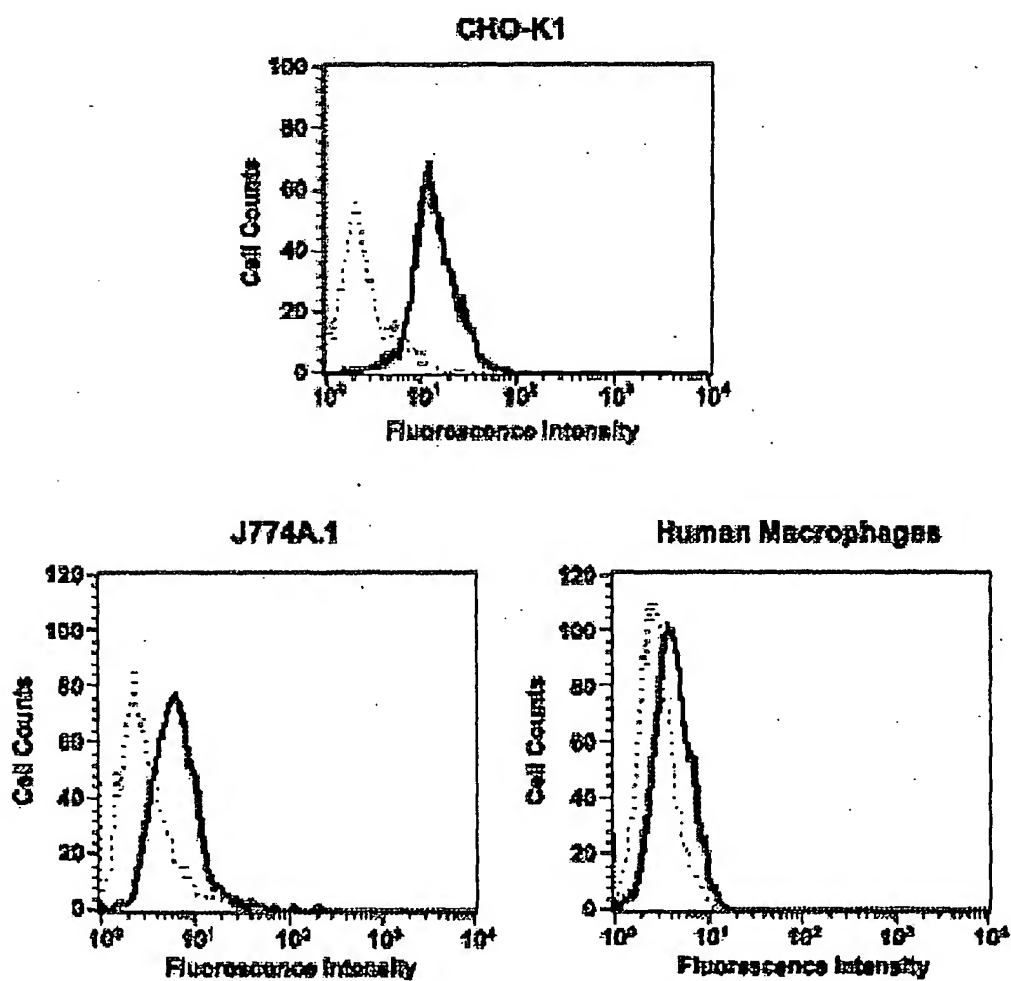


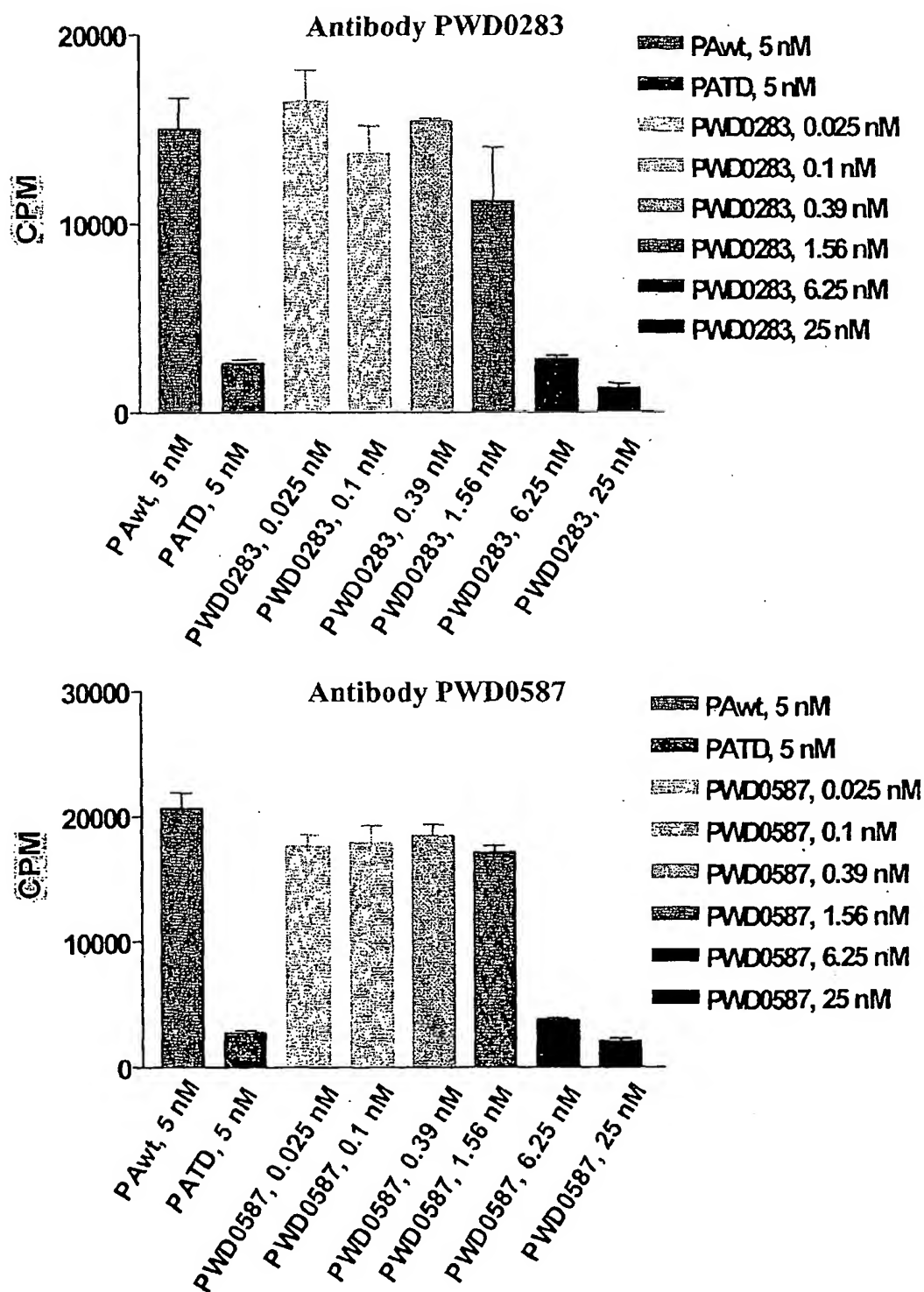
Figure 3: Rubidium Release Assay

Figure 4: Inhibition Of Cell Killing

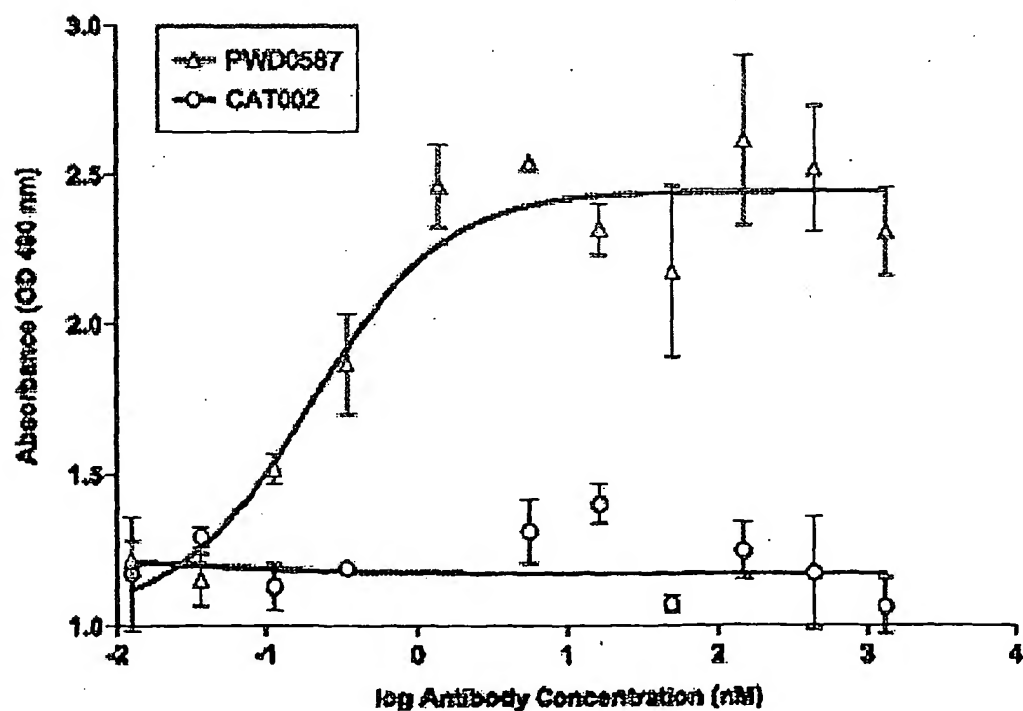
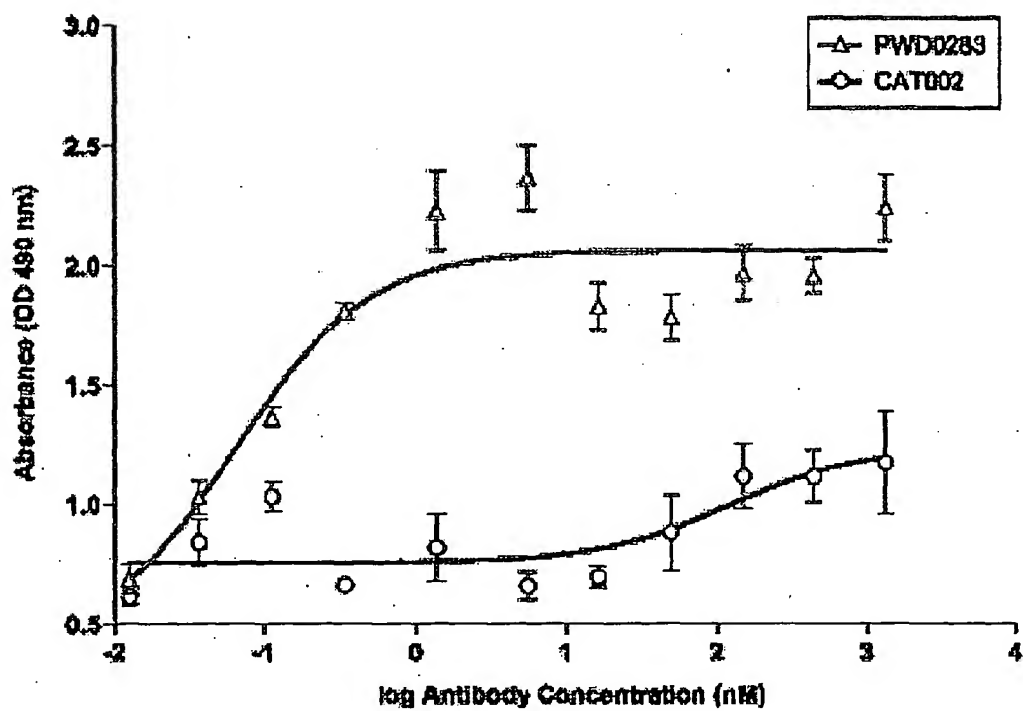


Figure 5: Effect of Prophylactic Administration of Anti-PA Monoclonal Antibodies 60 Minutes Prior to Lethal Toxin Exposure

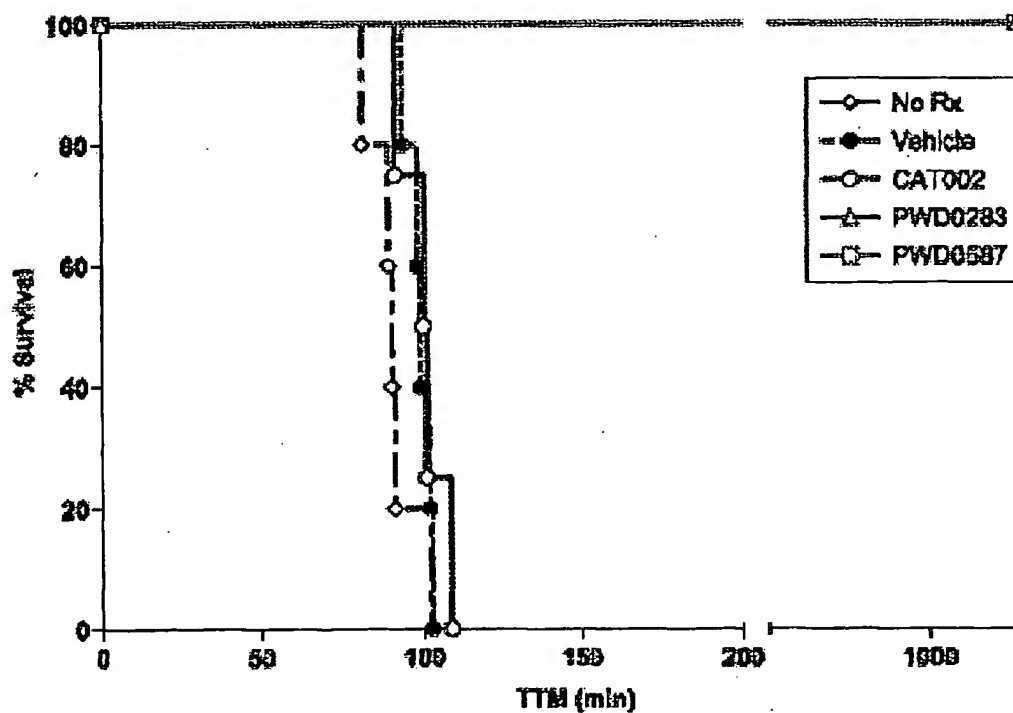


Figure 6
Survival Curves of New Zealand White Rabbits After
Inhalational Exposure to Lethal Dose of *B. anthracis* spores.

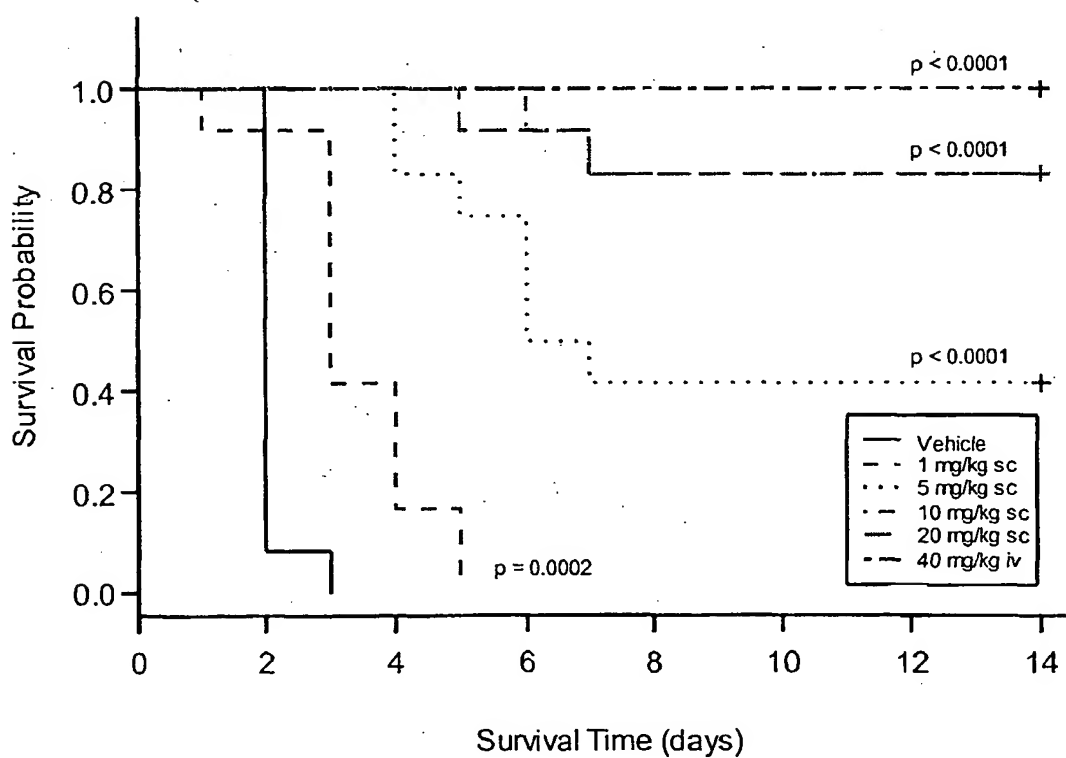
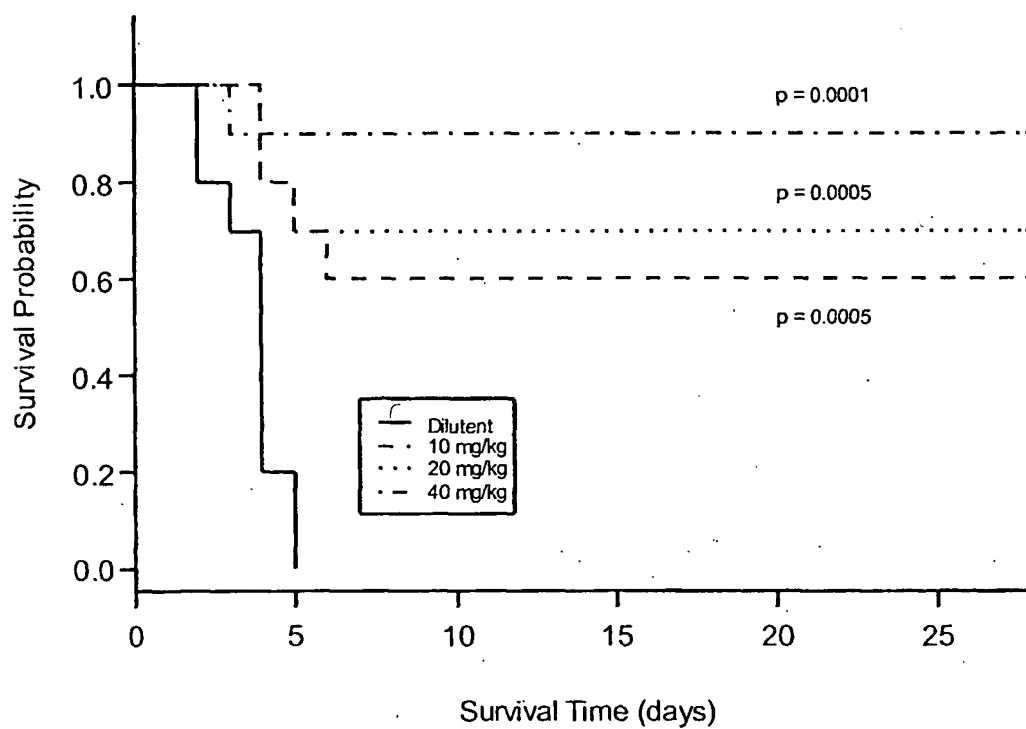


Figure 7
Survival Curves of Cynomolgus Monkeys After
Inhalational Exposure to Lethal Dose of *B. anthracis* spores.



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ANTIBODIES AGAINST PROTECTIVE ANTIGEN

RELATED APPLICATIONS

This application claims benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application Nos. 60/391,162, filed Jun. 26, 2002, 60/406,339, filed Aug. 28, 2002, 60/417,305, filed Oct. 10, 2002, 60/426,360, filed Nov. 15, 2002, 60/434,807, filed Dec. 20, 2002, 60/438,004, filed Jan. 6, 2003, 60/443,858 filed Jan. 31, 2003, 60/443,781, filed Jan. 31, 2003, 60/454,613 filed Mar. 17, 2003, and 60/468,651 filed May 8, 2003. Each of the aforementioned applications is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to antibodies and related molecules that specifically bind to the protective antigen (PA) of *Bacillus anthracis*. Such antibodies have uses, for example, in the prevention, detection and treatment of anthrax and/or anthrax related toxins. The invention also relates to nucleic acid molecules encoding anti-PA antibodies, vectors and host cells containing these nucleic acids, and methods for producing the same. The present invention relates to methods and compositions for preventing, detecting, diagnosing, treating or ameliorating anthrax and/or anthrax related toxins, comprising administering to an animal, preferably a human, an effective amount of one or more antibodies or fragments or variants thereof, or related molecules, that specifically bind to PA.

BACKGROUND OF THE INVENTION

Bacillus anthracis is a Gram-positive, aerobic, spore forming bacterium that is responsible for the deadly disease anthrax. There are three recognized routes of anthrax infection including cutaneous (through skin), gastrointestinal, and pulmonary (via inhalation) infection. Of the three ways to contract the disease, inhalation is the avenue that most frequently leads to the death of the patient.

Anthrax secretes a deadly three-component exotoxin which is comprised of three proteins, lethal factor (LF), edema factor (EF), and protective antigen (PA). The anthrax toxin is a bipartite toxin that contains A and B moieties, similar to that of diphtheria toxin and many clostridial toxins. The LF and EF proteins function as enzymatic A moieties of the toxin, while the PA protein functions as the B, or binding, moiety.

During the process of intoxication, PA binds to its cell surface receptor, (e.g., anthrax receptor (ATR) and/or capillary morphogenesis gene 2 (CMG2)) and is cleaved at the sequence RKKR (residues 193-196 of SEQ ID NO:2) by cell surface proteases such as furin. This cleavage releases a 20 kilodalton fragment of the PA protein, leaving a 63 kilodalton fragment of the PA protein bound to the cell surface (PA63). Some cleavage to the PA63 form may be mediated by serum proteases and occur prior to PA, in this case PA63, binding to the cell surface. Release of the 20 kilodalton PA fragment enables the PA63 fragment to multimerize into a heptameric ring structure and exposes a site on PA63 to which LF and EF bind with high affinity. The complex is then internalized by receptor-mediated endocytosis. Acidification of the vesicle causes conformational changes in the pA63 heptamer that result in transportation of LF and EF toxins across the endosomal membrane, after which they are released into the cytosol where they exert their cytotoxic effects. The edema factor

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(EF) component of edema toxin (EF+PA) is a calmodulin dependent adenylate cyclase whose action upsets cellular water homeostasis mechanisms, thereby resulting in swelling of infected tissues. The lethal factor (LF) moiety of lethal toxin (LF+PA) is a zinc metalloproteinase that inactivates mitogen activated protein kinase kinase in vitro. Lethal factor induces a hyperinflammatory condition in macrophages resulting in the production of proinflammatory cytokines including TNF-alpha and interleukin-1beta, which are responsible for shock and death of anthrax patients. For more detailed reviews of *Bacillus Anthracis* infection and anthrax toxin please see, e.g., *Critical Reviews in Microbiology* (2001) 27:167-200, *Medical Progress* (1999) 341:815-826, and *Microbes and Infection* (1999) 2:131-139, each of which are hereby incorporated by reference in their entireties.

There is a clear need, therefore, for identification and characterization of compositions, such as antibodies, that influence the biological activity of anthrax toxins.

SUMMARY OF THE INVENTION

The present invention encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that specifically bind to a PA polypeptide (SEQ ID NO:2) or polypeptide fragment or variant of PA.

The present invention relates to methods and compositions for preventing, treating or ameliorating anthrax disease and/or symptoms induced by anthrax related toxins (such as lethal toxin or edema toxin) comprising administering to an animal, preferably a human, an effective amount of one or more antibodies or fragments or variants thereof, or related molecules, that specifically bind to PA or a fragment or variant thereof. In specific embodiments, the present invention relates to methods and compositions for preventing, treating or ameliorating a disease or disorder associated with PA function, comprising administering to an animal, preferably a human, an effective amount of one or more antibodies or fragments or variants thereof, or related molecules, that specifically bind PA or a fragment or variant thereof.

In other embodiments, antibodies of the invention have a bactericidal effect on *B. anthracis* bacteria. By way of non-limiting example, antibodies of the invention may activate the classical complement pathway and/or enhance the activation of the alternative complement pathway which can lead to killing of bacterial cells. Alternatively, antibodies of the invention may opsonize *B. anthracis* bacteria. Opsonized bacteria then may be a target for antibody dependent cell-mediated cytotoxicity (ADCC). In another embodiment, antibodies of the invention may catalyze the generation of hydrogen peroxide from singlet molecular oxygen and water which chemical reaction results in the efficient killing of bacteria.

In specific embodiments, antibodies of the invention are administered in combination with other therapeutics or prophylactics such as a soluble form of an anthrax receptor (e.g., SEQ ID NO:3, described in *Nature* (2002) 414:225-229 (which is hereby incorporated by reference in its entirety), e.g., a polypeptide comprising amino acids 1-227 or 41-227 of SEQ ID NO:3) or a soluble form of the CMG2 receptor (SEQ ID NO:42, described in Scobie et al., *Proceedings of the National Academy of Sciences USA* (2003) 100:5170-5174 which is hereby incorporated by reference in its entirety, e.g., a polypeptide comprising amino acids 33-318 of SEQ ID NO:42). Other therapeutics or prophylactics that may be administered in combination with an antibody of the present invention include mutant forms of PA such as the EF/LF translocation deficient forms of PA described in International

Publication Number WO01/82788 and in Science (2001) 292:695-697, both of which are hereby incorporated by reference in their entireties. Other therapeutics or prophylactics that may be administered in combination with an antibody of the present invention include peptide inhibitors that block LF binding to PA such as the P1 peptide, or its polyvalent form described in Nature Biotechnology (2002) 19:958-961 which is hereby incorporated by reference in its entirety. Still other therapeutics or prophylactics that may be administered in combination with an antibody of the present invention include, but are not limited to antibiotics, anthrax vaccines, antibodies immunoreactive with LF, EF or other protein moieties of *Bacillus anthracis*.

Another embodiment of the present invention includes the use of the antibodies of the invention as a diagnostic tool to monitor the presence of PA.

Single chain Fv's (scFvs) that specifically bind PA polypeptide (SEQ ID NOS:48-65) have been identified. Thus, the invention encompasses these scFvs, listed in Table 1. In addition, the invention encompasses cell lines engineered to express antibodies corresponding to these scFvs which are deposited with the American Type Culture Collection ("ATCC") as of the dates listed in Table 1 and given the ATCC Deposit Numbers identified in Table 1. The ATCC is located at 10801 University Boulevard, Manassas, Va. 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for Purposes of Patent Procedure.

Further, the present invention encompasses the polynucleotides encoding the scFvs, as well as the amino acid sequences encoding the scFvs. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs (e.g., VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of the corresponding region of the recombinant antibody expressed by a cell line contained in an ATCC Deposit referred to in Table 1), that specifically bind to PA or fragments or variants thereof are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies and/or molecules. In specific embodiments, the present invention encompasses antibodies, or fragments or variants thereof, that bind to an epitope that comprises the RKKR sequence of amino acid residues 193 to 196 of SEQ ID NO:2. In other embodiments, the antibodies of the invention bind an epitope of PA and occlude access of proteases to the RKKR cleavage site of PA (amino acid residues 193 to 196 of SEQ ID NO:2). In other embodiments, antibodies of the invention neutralize the ability of PA to bind to a cellular anthrax receptor, e.g., ATR (SEQ ID NO:3) or CMG2 (SEQ ID NO:42). In other embodiments, antibodies of the invention neutralize the ability of the PA (particularly the PA63 form of PA) to form oligomers, and more specifically to form heptamers. And in still other embodiments, antibodies of the invention neutralize the ability of PA (particularly the PA63 form of PA) to bind to either EF or LF (SEQ ID NOS:4 or 5, respectively).

The present invention also provides anti-PA antibodies that are coupled to a detectable label, such as an enzyme, a fluorescent label, a luminescent label, or a bioluminescent label. The present invention also provides anti-PA antibodies that are coupled to a therapeutic or cytotoxic agent. The present invention also provides anti-PA antibodies that which are coupled, directly or indirectly, to a radioactive material.

In further embodiments, the antibodies of the invention have a dissociation constant (K_D) of 10^{-7} M or less. In preferred embodiments, the antibodies of the invention have a dissociation constant (K_D) of 10^{-9} M or less.

In further embodiments, antibodies of the invention have an off rate (k_{off}) of 10^{-3} /sec or less. In preferred embodiments, antibodies of the invention have an off rate (k_{off}) of 10^{-4} /sec or less. In other preferred embodiments, antibodies of the invention have an off rate (k_{off}) of 10^{-5} /sec or less.

The present invention also provides panels of antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants) wherein the panel members correspond to one, two, three, four, five, ten, fifteen, twenty, or more different antibodies of the invention (e.g., whole antibodies, Fabs, F(ab')₂ fragments, Fd fragments, disulfide-linked Fvs (sdFvs), anti-idiotypic (anti-Id) antibodies, and scFvs). The present invention further provides mixtures of antibodies, wherein the mixture corresponds to one, two, three, four, five, ten, fifteen, twenty, or more different antibodies of the invention (e.g., whole antibodies, Fabs, F(ab')₂ fragments, Fd fragments, disulfide-linked Fvs (sdFvs), anti-idiotypic (anti-Id) antibodies, and scFvs). The present invention also provides for compositions comprising, or alternatively consisting of, one, two, three, four, five, ten, fifteen, twenty, or more antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof). A composition of the invention may comprise, or alternatively consist of, one, two, three, four, five, ten, fifteen, twenty, or more amino acid sequences of one or more antibodies or fragments or variants thereof. Alternatively, a composition of the invention may comprise, or alternatively consist of, nucleic acid molecules encoding one or more antibodies of the invention.

The present invention also provides for fusion proteins comprising an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) of the invention, and a heterologous polypeptide (i.e., a polypeptide unrelated to an antibody or antibody domain). Nucleic acid molecules encoding these fusion proteins are also encompassed by the invention. A composition of the present invention may comprise, or alternatively consist of, one, two, three, four, five, ten, fifteen, twenty or more fusion proteins of the invention. Alternatively, a composition of the invention may comprise, or alternatively consist of, nucleic acid molecules encoding one, two, three, four, five, ten, fifteen, twenty or more fusion proteins of the invention.

The present invention also provides for a nucleic acid molecule(s), generally isolated, encoding an antibody (including molecules, such as scFvs, VH domains, or VL domains, that comprise, or alternatively consist of, an antibody fragment or variant thereof) of the invention. The present invention also provides a host cell transformed with a nucleic acid molecule of the invention and progeny thereof. The present invention also provides a method for the production of an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof) of the invention. The present invention further provides a method of expressing an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof) of the invention from a nucleic acid molecule. These and other aspects of the invention are described in further detail below.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 illustrates the ability of antibodies PWD0283 and PWD0587 to inhibit the binding of biotinylated PA to ATR.

FIG. 2 graphically depicts the binding of biotinylated-PA to CHO-K1 cells, J744.A murine macrophages, and human

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macrophages as determined by flow cytometry. The solid line depicts biotinylated-PA binding to cells; the dashed line depicts the background level.

FIG. 3 illustrates the ability of two antibodies PWD0283 and PWD0587 to inhibit pore formation by PA protein using the assay described in Example 5.

FIG. 4 illustrates the ability of antibodies PWD0283 and PWD0587 to inhibit lethal toxin (LT)-mediated cell killing. Data are presented as mean \pm SD absorbance at 490 nm.

FIG. 5 illustrates the effect of prophylactic intravenous administration of PWD0283 and PWD0587 60 minutes prior to exposure of male Fisher 344 rats to Lethal Toxin. CAT 002 is an isotype-matched (IgG1) negative control antibody. A single intravenous injection of PWD0283 or PWD0587 60 minutes prior to injection of lethal toxin provided 100% survival at 24 hours with no apparent ill effects. In contrast, a single injection of the negative control mAb, CAT002, provided no protection with 0% survival and an average TTM of 100 minutes. Vehicle or no study agent also provided no protection with 0% survival and an average TTM of 99 minutes and 91 minutes, respectively.

FIG. 6 shows the 14 day survival curves of the New Zealand White Rabbits (n=12) that received:

- a) no treatment (vehicle) two days prior to;
- b) prophylactic treatment (1, 5, 10, or 20 mg/kg sc) two days prior to; or
- c) therapeutic treatment (40 mg/kg iv) within 1 hour after challenge via aerosol inhalation of approximately $195 \times LD_{50}$ of *B. anthracis* spores. Experimental details are described more fully in Example 11. Statistical p-values were obtained from a 2-sided log-rank test. The p-values for the comparison among all groups are <0.0001 , regardless of inclusion or exclusion of the 40 mg/kg iv group in the analysis. The p-values marked in the graph are for the comparison versus the vehicle control group.

FIG. 7 shows the 28 day survival curves of cynomolgus monkeys (n=10 per group) that received no treatment (vehicle) or prophylactic treatment via subcutaneous administration of anti-PA monoclonal antibody PWD0587 (10, 20 or 40 mg/kg), two days prior to challenge via aerosol inhalation of approximately $186 \times LD_{50}$ of *B. anthracis* spores. Experimental details are described more fully in Example 12. Statistical p-values were obtained from a 2-sided log-rank test. The P values for the comparison among all groups are <0.0001 . The P values marked in the graph are for the comparison versus the vehicle control group.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that specifically binds an antigen. As such, the term antibody encompasses not only whole antibody molecules, but also antibody multimers and antibody fragments, as well as variants (including derivatives) of antibodies, antibody multimers and antibody fragments. Examples of molecules which are described by the term "antibody" herein include, but are not limited to: single chain Fvs (scFvs), Fab fragments, Fab' fragments, F(ab')₂, disulfide linked Fvs (sdFvs), Fvs, and fragments comprising or alternatively consisting of, either a VL or a VH domain. The term "single chain Fv" or "scFv" as used herein refers to a polypeptide comprising a VL domain of antibody linked to a VH domain of an antibody.

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Antibodies of the invention include, but are not limited to, monoclonal, multispecific, human or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), intracellularly-made antibodies (i.e., intrabodies), and epitope-binding fragments of any of the above. The immunoglobulin molecules of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG₁, IgG₂, IgG₃, IgG₄, IgA₁, and IgA₂) or subclass of immunoglobulin molecule. Preferably, an antibody of the invention comprises, or alternatively consists of, a VH domain, VH CDR, VL domain, or VL CDR having an amino acid sequence of any one of the cell lines in the ATCC Deposits referred to in Table 1, or a fragment or variant thereof. In a preferred embodiment, the immunoglobulin is an IgG1 isotype. In another preferred embodiment, the immunoglobulin is an IgG4 isotype. Immunoglobulins may have both a heavy and light chain. An array of IgG, IgE, IgM, IgD, IgA, and IgY heavy chains may be paired with a light chain of the kappa or lambda forms. Antibodies of the invention may also include multimeric forms of antibodies. For example, antibodies of the invention may take the form of antibody dimers, trimers, or higher-order multimers of monomeric immunoglobulin molecules. Dimers of whole immunoglobulin molecules or of F(ab')₂ fragments are tetravalent, whereas dimers of Fab fragments or scFv molecules are bivalent. Individual monomers within an antibody multimer may be identical or different, i.e., they may be heteromeric or homomeric antibody multimers. For example, individual antibodies within a multimer may have the same or different binding specificities.

Multimerization of antibodies may be accomplished through natural aggregation of antibodies or through chemical or recombinant linking techniques known in the art. For example, some percentage of purified antibody preparations (e.g., purified IgG1 molecules) spontaneously form protein aggregates containing antibody homodimers, and other higher-order antibody multimers. Alternatively, antibody homodimers may be formed through chemical linkage techniques known in the art. For example, heterobifunctional crosslinking agents including, but not limited to, SMCC [succinimidyl 4-(maleimidomethyl)cyclohexane-1 carboxylate] and SATA [N-succinimidyl S-acetylthioacetate] (available, for example, from Pierce Biotechnology, Inc. (Rockford, Ill.)) can be used to form antibody multimers. An exemplary protocol for the formation of antibody homodimers is given in Ghetie et al., Proceedings of the National Academy of Sciences USA (1997) 94:7509-7514, which is hereby incorporated by reference in its entirety. Antibody homodimers can be converted to Fab'2 homodimers through digestion with pepsin. Another way to form antibody homodimers is through the use of the autophilic T15 peptide described in Zhao and Kohler, The Journal of Immunology (2002) 25:396-404, which is hereby incorporated by reference in its entirety.

Alternatively, antibodies can be made to multimerize through recombinant DNA techniques. IgM and IgA naturally form antibody multimers through the interaction with the mature J chain polypeptide (e.g., SEQ ID NO:44). Non-IgA or non-IgM molecules, such as IgG molecules, can be engineered to contain the J chain interaction domain of IgA or IgM, thereby conferring the ability to form higher order multimers on the non-IgA or non-IgM molecules. (see, for example, Chintalacharuvu et al., (2001) Clinical Immunology 101:21-31. and Frigerio et al., (2000) Plant Physiology 123:1483-94, both of which are hereby incorporated by reference in their entireties.) IgA dimers are naturally secreted into the lumen of mucosa-lined organs. This secretion is

mediated through interaction of the J chain with the polymeric IgA receptor (pIgR) on epithelial cells. If secretion of an IgA form of an antibody (or of an antibody engineered to contain a J chain interaction domain) is not desired, it can be greatly reduced by expressing the antibody molecule in association with a mutant J chain that does not interact well with pIgR (e.g., SEQ ID NOS:45-47; Johansen et al., *The Journal of Immunology* (2001) 167:5185-5192 which is hereby incorporated by reference in its entirety). Expression of an antibody with one of these mutant J chains will reduce its ability to bind to the polymeric IgA receptor on epithelial cells, thereby reducing transport of the antibody across the epithelial cell and its resultant secretion into the lumen of mucosa lined organs. ScFv dimers can also be formed through recombinant techniques known in the art; an example of the construction of scFv dimers is given in Goel et al., (2000) *Cancer Research* 60:6964-6971 which is hereby incorporated by reference in its entirety. Antibody multimers may be purified using any suitable method known in the art, including, but not limited to, size exclusion chromatography.

By "isolated antibody" is intended an antibody removed from its native environment. Thus, an antibody produced by, purified from and/or contained within a hybridoma and/or a recombinant host cell is considered isolated for purposes of the present invention.

Unless otherwise defined in the specification, specific binding by an antibody to PA means that an antibody binds PA but does not significantly bind to (i.e., cross react with) proteins other than PA, such as other proteins in the same family of proteins). An antibody that binds PA protein and does not cross-react with other proteins is not necessarily an antibody that does not bind said other proteins in all conditions; rather, the PA-specific antibody of the invention preferentially binds PA compared to its ability to bind said other proteins such that it will be suitable for use in at least one type of assay or treatment, i.e., give low background levels or result in no unreasonable adverse effects in treatment. It is well known that the portion of a protein bound by an antibody is known as the epitope. An epitope may either be linear (i.e., comprised of sequential amino acids residues in a protein sequences) or conformational (i.e., comprised of one or more amino acid residues that are not contiguous in the primary structure of the protein but that are brought together by the secondary, tertiary or quaternary structure of a protein). Given that PA-specific antibodies bind to epitopes of PA, an antibody that specifically binds PA may or may not bind fragments of PA and/or variants of PA (e.g., proteins that are at least 90% identical to PA) depending on the presence or absence of the epitope bound by a given PA-specific antibody in the PA fragment or variant. Likewise, PA-specific antibodies of the invention may bind species orthologues of PA (including fragments thereof) depending on the presence or absence of the epitope recognized by the antibody in the orthologue. Additionally, PA-specific antibodies of the invention may bind modified forms of PA, for example, PA fusion proteins. In such a case when antibodies of the invention bind PA fusion proteins, the antibody must make binding contact with the PA moiety of the fusion protein in order for the binding to be specific. Antibodies that specifically bind to PA can be identified, for example, by immunoassays or other techniques known to those of skill in the art, e.g., the immunoassays described in the Examples below.

Antibodies of the invention may also include multimeric forms of antibodies. For example, antibodies of the invention may take the form of antibody dimers, trimers, or higher-order multimers of monomeric immunoglobulin molecules. Dimers of whole immunoglobulin molecules or of F(ab')₂ fragments are tetravalent, whereas dimers of Fab fragments or scFv molecules are bivalent. Individual monomers within an antibody multimer may be identical or different, i.e., they may be heteromeric or homomeric antibody multimers. For example, individual antibodies within a multimer may have the same or different binding specificities. Multimerization of antibodies may be accomplished through natural aggregation of antibodies or through chemical or recombinant linking techniques known in the art. For example, some percentage of purified antibody preparations (e.g., purified IgG1 molecules) spontaneously form protein aggregates containing antibody homodimers, and other higher-order antibody multimers. Alternatively, antibody homodimers may be formed through chemical linkage techniques known in the art. For example, heterobifunctional crosslinking agents including, but not limited to, SMCC [succinimidyl 4-(maleimidoethyl)cyclohexane-1-carboxylate] and SATA [N-succinimidyl S-acetylthioacetate] (available, for example, from Pierce Biotechnology, Inc. (Rockford, Ill.)) can be used to form antibody multimers. An exemplary protocol for the formation of antibody homodimers is given in Ghetie et al., *Proceedings of the National Academy of Sciences USA* (1997) 94:7509-7514, which is hereby incorporated by reference in its entirety. Antibody homodimers can be converted to Fab'2 homodimers through digestion with pepsin. Alternatively, antibodies can be made to multimerize through recombinant DNA techniques. IgM and IgA naturally form antibody multimers through the interaction with the J chain polypeptide. Non-IgA or non-IgM molecules, such as IgG molecules, can be engineered to contain the J chain interaction domain of IgA or IgM, thereby conferring the ability to form higher order multimers on the non-IgA or non-IgM molecules. (see, for example, Chintalacharuvu et al., (2001) *Clinical Immunology* 101:21-31 and Frigerio et al., (2000) *Plant Physiology* 123:1483-94, both of which are hereby incorporated by reference in their entireties.) ScFv dimers can also be formed through recombinant techniques known in the art; an example of the construction of scFv dimers is given in Goel et al., (2000) *Cancer Research* 60:6964-6971, which is hereby incorporated by reference in its entirety. Antibody multimers may be purified using any suitable method known in the art, including, but not limited to, size exclusion chromatography.

The term "variant" as used herein refers to a polypeptide that possesses a similar or identical amino acid sequence as a PA polypeptide, a fragment of a PA polypeptide, an anti-PA antibody or antibody fragment thereof. A variant having a similar amino acid sequence refers to a polypeptide that satisfies at least one of the following: (a) a polypeptide comprising, or alternatively consisting of, an amino acid sequence that is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 99% identical to the amino acid sequence of PA polypeptide (SEQ ID NO:2), a fragment of a PA polypeptide, an anti-PA antibody or antibody fragment thereof (including a VH domain, VHCDR, VL domain, or VLCDR having an amino acid sequence of any one or more scFvs or recombinant antibodies expressed by the cell lines in the ATCC Deposits referred to in Table 1) described herein; (b) a polypeptide encoded by a nucleotide sequence, the complementary sequence of which hybridizes under stringent

conditions to a nucleotide sequence encoding PA (SEQ ID NO:2), a fragment of a PA polypeptide, an anti-PA antibody or antibody fragment thereof (including a VH domain, VHCDR, VL domain, or VLCDR having an amino acid sequence of any one of the scFvs referred to in Table 1), described herein, of at least 5 amino acid residues, at least 10 amino acid residues, at least 15 amino acid residues, at least 20 amino acid residues, at least 25 amino acid residues, at least 30 amino acid residues, at least 40 amino acid residues, at least 50 amino acid residues, at least 60 amino acid residues, at least 70 amino acid residues, at least 80 amino acid residues, at least 90 amino acid residues, at least 100 amino acid residues, at least 125 amino acid residues, or at least 150 amino acid residues; and (c) a polypeptide encoded by a nucleotide sequence that is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 99%, identical to the nucleotide sequence encoding a PA polypeptide, a fragment of a PA polypeptide, an anti-PA antibody or antibody fragment thereof (including a VH domain, VHCDR, VL domain, or VLCDR having an amino acid sequence of any one or more scFvs or recombinant antibodies expressed by the cell lines in the ATCC Deposits referred to in Table 1), described herein. A polypeptide with similar structure to a PA polypeptide, a fragment of a PA polypeptide, an anti-PA antibody or antibody fragment thereof, described herein refers to a polypeptide that has a similar secondary, tertiary or quaternary structure of a PA polypeptide, a fragment of a PA polypeptide, an anti-PA antibody, or antibody fragment thereof, described herein. The structure of a polypeptide can be determined by methods known to those skilled in the art, including but not limited to, X-ray crystallography, nuclear magnetic resonance, and crystallographic electron microscopy. Preferably, a variant PA polypeptide, a variant fragment of a PA polypeptide, or a variant anti-PA antibody and/or antibody fragment possesses similar or identical function and/or structure as the reference PA polypeptide, the reference fragment of a PA polypeptide, or the reference anti-PA antibody and/or antibody fragment, respectively.

To determine the percent identity of two amino acid sequences or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino acid or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide at the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., % identity number of identical overlapping positions/total number of positions \times 100%). In one embodiment, the two sequences are the same length.

The determination of percent identity between two sequences can be accomplished using a mathematical algorithm known to those of skill in the art. An example of a mathematical algorithm for comparing two sequences is the algorithm of Karlin and Altschul *Proc. Natl. Acad. Sci. USA* 87:2264-2268 (1990), modified as in Karlin and Altschul *Proc. Natl. Acad. Sci. USA* 90:5873-5877 (1993). The BLASTn and BLASTx programs of Altschul, et al. *J. Mol. Biol.* 215:403-410 (1990) have incorporated such an algo-

ri thm. BLAST nucleotide searches can be performed with the BLASTn program (score=100, wordlength=12) to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the BLASTx program (score=50, wordlength=3) to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al. *Nucleic Acids Res.* 25:3589-3402 (1997). Alternatively, PSI-BLAST can be used to perform an iterated search which detects distant relationships between molecules (Id.). When utilizing BLAST, Gapped BLAST, and PSI-BLAST programs, the default parameters of the respective programs (e.g., BLASTx and BLASTn) can be used.

Another example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, CABIOS (1989). The ALIGN program (version 2.0) which is part of the GCG sequence alignment software package has incorporated such an algorithm. Other algorithms for sequence analysis known in the art include ADVANCE and ADAM as described in Torellis and Robotti *Comput. Appl. Biosci.*, 10:3-5 (1994); and FASTA described in Pearson and Lipman *Proc. Natl. Acad. Sci.* 85:2444-8 (1988). Within FASTA, ktup is a control option that sets the sensitivity and speed of the search.

The term "derivative" as used herein, refers to a variant polypeptide of the invention that comprises, or alternatively consists of, an amino acid sequence of a PA polypeptide, a fragment of a PA polypeptide, or an antibody of the invention that specifically binds to a PA polypeptide, which has been altered by the introduction of amino acid residue substitutions, deletions or additions. The term "derivative" as used herein also refers to a PA polypeptide, a fragment of a PA polypeptide, an antibody that specifically binds to a PA polypeptide which has been modified, e.g., by the covalent attachment of any type of molecule to the polypeptide. For example, but not by way of limitation, a PA polypeptide, a fragment of a PA polypeptide, or an anti-PA antibody, may be modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a; cellular ligand or other protein, etc. A derivative of a PA polypeptide, a fragment of a PA polypeptide, or an anti-PA antibody, may be modified by chemical modifications using techniques known to those of skill in the art, including, but not limited to, specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Further, a derivative of a PA polypeptide, a fragment of a PA polypeptide, or an anti-PA antibody, may contain one or more non-classical amino acids. A polypeptide derivative possesses a similar or identical function as a PA polypeptide, a fragment of a PA polypeptide, or an anti-PA antibody, described herein.

The term "fragment" as used herein refers to a polypeptide comprising an amino acid sequence of at least 5 amino acid residues, at least 10 amino acid residues, at least 15 amino acid residues, at least 20 amino acid residues, at least 25 amino acid residues, at least 30 amino acid residues, at least 35 amino acid residues, at least 40 amino acid residues, at least 45 amino acid residues, at least 50 amino acid residues, at least 60 amino acid residues, at least 70 amino acid residues, at least 80 amino acid residues, at least 90 amino acid residues, at least 100 amino acid residues, at least 125 amino acid residues, at least 150 amino acid residues, at least 175 amino

acid residues, at least 200 amino acid residues, or at least 250 amino acid residues, of the amino acid sequence of PA, or an anti-PA antibody (including molecules such as scFv's, that comprise, or alternatively consist of, antibody fragments or variants thereof) that specifically binds to PA.

The term "host cell" as used herein refers to the particular subject cell transfected with a nucleic acid molecule and the progeny or potential progeny of such a cell. Progeny may not be identical to the parent cell transfected with the nucleic acid molecule due to mutations or environmental influences that may occur in succeeding generations or integration of the nucleic acid molecule into the host cell genome.

Antibodies of the present invention are preferably provided in an isolated form, and preferably are substantially purified. By "isolated" is intended an antibody removed from its native environment. Thus, for example, an antibody produced and/or contained, within a recombinant host cell is considered isolated for purposes of the present invention.

Antibody Structure

The basic antibody structural unit is known to comprise a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kilodalton) and one "heavy" chain (about 50-70 kilodalton). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. Herein the terms "heavy chain" and "light chain" refer to the heavy and light chains of an antibody unless otherwise specified. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function. Human light chains are classified as kappa and lambda light chains. Heavy chains are classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. See generally, *Fundamental Immunology* Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989)) (incorporated by reference in its entirety for all purposes). The variable regions of each light/heavy chain pair form the antibody binding site.

Thus, an intact IgG antibody has two binding sites. Except in bifunctional or bispecific antibodies, the two binding sites are the same.

The chains all exhibit the same general structure of relatively conserved framework regions (FR) joined by three hyper variable regions, also called complementarity determining regions or CDRs. The CDRs from the heavy and the light chains of each pair are aligned by the framework regions, enabling binding to a specific epitope. From N-terminal to C-terminal, both light and heavy chains comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is in accordance with the definitions of Kabat *Sequences of Proteins of Immunological Interest* (National Institutes of Health, Bethesda, Md. (1987 and 1991)), or Chothia & Lesk, *J. Mol. Biol.* 196:901-917 (1987); Chothia et al., *Nature* 342:878-883 (1989).

A bispecific or bifunctional antibody is an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. Bispecific antibodies can be produced by a variety of methods including fusion of hybridomas or linking of Fab' fragments. See, e.g., Songsivilai & Lachmann *Clin. Exp. Immunol.* 79: 315-321 (1990); Kostelny et al. *J. Immunol.* 148:1547-1553 (1992). In addition, bispecific antibodies may be formed as "diabodies" (Holliger et al. "Dia-

bodies': small bivalent and bispecific antibody fragments" PNAS USA 90:6444-6448 (1993)) or "Janusins" (Traunecker et al. "Bispecific single chain molecules (Janusins) target cytotoxic lymphocytes on HIV infected cells" *EMBO J* 10:3655-3659 (1991) and Traunecker et al. "Janusin: new molecular design for bispecific reagents" *Int J Cancer Suppl* 7:51-52 (1992)).

Production of bispecific antibodies can be a relatively labor intensive process compared with production of conventional antibodies and yields and degree of purity are generally lower for bispecific antibodies. Bispecific antibodies do not exist in the form of fragments having a single binding site (e.g., Fab, Fab', and Fv).

Anti-PA Antibodies

Using phage display technology, single chain antibody molecules ("scFvs") that specifically bind to PA (or fragments or variants thereof) have been identified (Example 1).

Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs (e.g., VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of the corresponding region of the antibody expressed by a cell line contained in an ATCC Deposit referred to in Table 1), that specifically bind to PA (or fragments or variants thereof) are also encompassed by the invention, as are nucleic acid molecules that encode these scFvs, and/or molecules.

In particular, the invention relates to scFvs comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of SEQ ID NOs: 48-56, preferably SEQ ID NOs: 50 and 53 as referred to in Table 1 below. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs (e.g., VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that specifically bind to PA are also encompassed by the invention, as are nucleic acid molecules that encode these scFvs, and/or molecules (e.g., SEQ ID NOs: 57-65).

The present invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that specifically bind to a polypeptide or a polypeptide fragment of PA. In particular, the invention provides antibodies corresponding to the scFvs referred to in Table 1. Such scFvs may routinely be "converted" to immunoglobulin molecules by inserting, for example, the nucleotide sequences encoding the VH and/or VL domains of the scFv into an expression vector containing the constant domain sequences and engineered to direct the expression of the immunoglobulin molecule, as described in more detail in Example 6 below.

NS0 cell lines that express IgG1 antibodies that comprise the VH and VL domains of scFvs of the invention have been deposited with the American Type Culture Collection ("ATCC") on the dates listed in Table 1 and given the ATCC Deposit Numbers identified in Table 1. The ATCC is located at 10801 University Boulevard, Manassas, Va. 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for purposes of patent procedure.

Accordingly, in one embodiment, the invention provides antibodies that comprise the VH and VL domains of scFvs of the invention.

In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line NSO PA 2973 (PWD0587) #240-22 (See Table 1).

TABLE 1

Anti-PA scFvs													
scFv	scFv protein SEQ ID NO:	scFv DNA SEQ ID NO:	AAs of VH Domain	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	AAs of VL Domain	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	Cell Line Expressing antibody	ATCC Deposit Number	ATCC Deposit Date
PWB2447	48	57	1-125	26-35	50-66	99-114	140-248	162-172	188-194	227-237			
PWC2004	49	58	1-123	26-35	50-66	99-112	140-251	162-175	191-197	230-240			
PWD0283	50	59	1-118	26-35	50-66	99-107	136-246	158-170	186-192	225-235			
PWD0323	51	60	1-117	26-35	50-66	99-106	134-244	156-168	184-190	223-233			
PWD0422	52	61	1-117	26-35	50-66	99-106	134-244	156-168	184-190	223-233			
PWD0587	53	62	1-117	26-35	50-66	99-106	134-244	156-168	184-190	223-233	NSO PA 2973 (PWD0587) #240-22	PTA-4796	Nov. 11, 2002
PWD0791	54	63	1-120	26-35	50-66	99-109	138-248	160-172	188-194	227-237			
PHD2222	55	64	1-117	26-35	50-66	99-106	134-244	156-168	184-190	223-233			
PHD2581	56	65	1-117	26-35	50-66	99-106	134-244	156-168	184-190	223-233			

The present invention encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that specifically bind to a PA polypeptide or a fragment, variant, or fusion protein thereof. A PA polypeptide includes, but is not limited to, PA (SEQ ID NO:2).

Protective Antigen

Antibodies of the present invention bind PA polypeptide or fragments or variants thereof. The following section describes the PA polypeptides, fragments and variants that may be bound by the antibodies of the invention in more detail.

The PA protein is a 764 amino acid protein (SEQ ID NO:2) comprising a signal sequence from amino acid residues 1-29, and a 735 amino acid secreted protein which undergoes further process upon binding to an anthrax receptor, (e.g., ATR or CMG2) on the cell surface. The 735 amino acid secreted protein, also known as PA83 because it has a molecular weight of approximately 83 kilodaltons, has a structure that is largely made up of antiparallel beta pleated sheets with only a few short alpha-helices. The protein can be divided into four domains: Domain I (amino acid residues 30-287 of SEQ ID NO:2), Domain II (amino acid residues 288-516 of SEQ ID NO:2), Domain III (amino acid residues 517-624 of SEQ ID NO:2), and Domain IV (amino acid residues 625-764) of SEQ ID NO:2). In its native form, Domain I contains two calcium ions and the protease cleavage site RKKR at amino acid residues 193-196 of SEQ ID NO:2. Thus, Domain I contains the entire 20 kilodalton fragment (PA20, amino acid residues 30-196 of SEQ ID NO:2) that is cleaved off of PA upon binding to an anthrax receptor (e.g., ATR or CMG2) at the cell surface. That portion of Domain I that remains after cleavage of PA20 forms the N terminus of active PA63 and may be involved in binding LF and EF. Domain II is the heptamerization domain and also contains a large flexible loop that is implicated in membrane insertion. Domain III, is small and its function is not clearly understood. Domain IV is the receptor binding domain.

Thus, in specific embodiments, antibodies of the invention may bind the intact 735 amino acid secreted form of PA (PA83), polypeptides that comprise or alternatively consist of the PA63 protein, the PA20 fragment, and/or any one or more of domains I, II, III, or W. In preferred embodiments, antibodies of the invention bind PA83 and prevent its cleavage of the PA20 fragment from the PA63 fragment by proteases. In

other embodiments, antibodies of the invention bind the PA63 form of PA and prevent oligomerization, and in particular heptamerization of PA63.

In certain embodiments, the antibodies of the present invention specifically bind PA polypeptide. An antibody that specifically binds PA may, in some embodiments, bind fragments, variants (including species orthologs of PA), multimers or modified forms of PA. For example, an antibody specific for PA may bind the PA moiety of a fusion protein comprising all or a portion of PA.

PA proteins may be found as monomers or multimers (i.e., dimers, trimers, tetramers, and higher multimers). Accordingly, the present invention relates to antibodies that bind PA proteins found as monomers or as part of multimers. In specific embodiments, antibodies of the invention bind PA monomers, dimers, trimers or heptamers. In additional embodiments, antibodies of the invention bind at least dimers, at least trimers, or at least tetramers containing one or more PA polypeptides.

Antibodies of the invention may bind PA homomers or heteromers. As used herein, the term homomer, refers to a multimer containing only PA proteins of the invention (including PA fragments such as PA63, variants, and fusion proteins, as described herein). These homomers may contain PA proteins having identical or different polypeptide sequences. In a specific embodiment, a homomer of the invention is a multimer containing only PA proteins having an identical polypeptide sequence. In another specific embodiment, antibodies of the invention bind PA homomers containing PA proteins having different polypeptide sequences. In specific embodiments, antibodies of the invention bind a PA homodimer (e.g., containing PA proteins having identical or different polypeptide sequences). In additional embodiments, antibodies of the invention bind at least a homodimer, at least a homotrimer, or at least a homotetramer of PA.

In specific embodiments antibodies of the present invention bind PA homoheptamers.

As used herein, the term heteromer refers to a multimer containing heterologous proteins (i.e., proteins containing polypeptide sequences that do not correspond to a polypeptide sequences encoded by the PA gene) in addition to the PA proteins of the invention. In a specific embodiment, antibodies of the invention bind a heterodimer, a heterotrimer, or a heterotetramer. In additional embodiments, the antibodies of

the invention bind at least a heterodimer, at least a heterotrimer, or at least a heterotetramer containing one or more PA polypeptides.

In specific embodiments, antibodies of the present invention bind a PA heteroheptamer.

Antibodies of the invention may bind PA multimers that are the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus, in one embodiment, antibodies of the invention may bind PA multimers, such as, for example, homoheptamers, that are formed when PA proteins (such as PA63 polypeptide monomers) contact one another in solution. In another embodiment, antibodies of the invention may bind heteromultimers, such as, for example, heteroheptamers, that are formed when proteins of the invention contact antibodies to the PA polypeptides (including antibodies to the heterologous polypeptide sequence in a fusion protein) in solution. In other embodiments, multimers bound by one or more antibodies of the invention are formed by covalent associations with and/or between the PA proteins of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence of the protein (e.g., the polypeptide sequence recited in SEQ ID NO:2). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences of the proteins which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a PA fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein (see, e.g., U.S. Pat. No. 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a PA-Fc or PA-human serum albumin (PA-HSA) fusion protein (as described herein).

Antibodies of the invention may bind PA multimers generated using chemical techniques known in the art. For example, proteins desired to be contained in the multimers of the invention may be chemically cross-linked using linker molecules and linker molecule length optimization techniques known in the art (see, e.g., U.S. Pat. No. 5,478,925, which is herein incorporated by reference in its entirety). Additionally, multimers that antibodies of the invention may bind can be generated using techniques known in the art to form one or more inter-molecule cross-links between the cysteine residues located within the polypeptide sequence of the proteins desired to be contained in the multimer (see, e.g., U.S. Pat. No. 5,478,925, which is herein incorporated by reference in its entirety). Further, proteins that antibodies of the invention may bind can be routinely modified by the addition of cysteine or biotin to the C terminus or N-terminus of the polypeptide sequence of the protein and techniques known in the art may be applied to generate multimers containing one or more of these modified proteins (see, e.g., U.S. Pat. No. 5,478,925, which is herein incorporated by reference in its entirety). Additionally, techniques known in the art may be applied to generate liposomes containing the protein components desired to be contained in the multimer that antibodies of the invention may bind (see, e.g., U.S. Pat. No. 5,478,925, which is herein incorporated by reference in its entirety).

Alternatively, multimers that antibodies of the invention may bind can be generated using genetic engineering techniques known in the art. In one embodiment, proteins contained in multimers that may be bound by one or more antibodies of the invention are produced recombinantly using

fusion protein technology described herein or otherwise known in the art (see, e.g., U.S. Pat. No. 5,478,925, which is herein incorporated by reference in its entirety). In a specific embodiment, polynucleotides coding for a homodimer that may be bound by one or more antibodies of the invention are generated by ligating a polynucleotide sequence encoding a PA polypeptide to a sequence encoding a linker polypeptide and then further to a synthetic polynucleotide encoding the translated product of the polypeptide in the reverse orientation from the original C-terminus to the N-terminus (lacking the leader sequence) (see, e.g., U.S. Pat. No. 5,478,925, which is herein incorporated by reference in its entirety). In another embodiment, recombinant techniques described herein or otherwise known in the art are applied to generate recombinant PA polypeptides which contain a transmembrane domain and which can be incorporated by membrane reconstitution techniques into liposomes (see, e.g., U.S. Pat. No. 5,478,925, which is herein incorporated by reference in its entirety). In another embodiment, two or more PA polypeptides are joined through synthetic linkers (e.g., peptide, carbohydrate or soluble polymer linkers). Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple PA polypeptides separated by peptide linkers may be produced using conventional recombinant DNA technology. In specific embodiments, antibodies of the invention bind proteins comprising multiple PA polypeptides separated by peptide linkers.

Another method for preparing multimer PA polypeptides involves use of PA polypeptides fused to a leucine zipper or isoleucine polypeptide sequence. Leucine zipper domains and isoleucine zipper domains are polypeptides that promote multimerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., *Science* 240:1759, (1988)), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble multimeric PA proteins are those described in PCT application WO 94/10308, hereby incorporated by reference. Recombinant fusion proteins comprising a soluble PA polypeptide fused to a peptide that dimerizes or trimerizes in solution are expressed in suitable host cells, and the resulting soluble multimeric PA is recovered from the culture supernatant using techniques known in the art. In specific embodiments, antibodies of the invention bind PA-leucine zipper fusion protein monomers and/or PA-leucine zipper fusion protein multimers.

Antibodies that bind PA receptor polypeptides may bind them as isolated polypeptides or in their naturally occurring state. By "isolated polypeptide" is intended a polypeptide removed from its native environment. Thus, a polypeptide produced and/or contained within a recombinant host cell is considered isolated for purposes of the present invention. Also intended as an "isolated polypeptide" are polypeptides that have been purified, partially or substantially, from a recombinant host cell. For example, a recombinantly produced version of the PA polypeptide may be substantially purified by the one-step method described in Smith and Johnson, *Gene* 67:31-40 (1988). Thus, antibodies of the present invention may bind recombinantly and/or naturally produced PA polypeptides. In a specific embodiment, antibodies of the present invention bind a PA secreted by a cell, preferably a bacterial cell, comprising a polynucleotide encoding amino acids 1 to 764 of SEQ ID NO:2 operably associated with a regulatory sequence that controls gene

expression. In a specific embodiment, antibodies of the present invention bind PA purified from a bacterial cell culture, wherein said PA is encoded by a polynucleotide encoding amino acids 1 to 764 of SEQ ID NO:2 operably associated with a regulatory sequence that controls expression of said polynucleotide. In other specific embodiments, antibodies of the present invention bind a PA polypeptide expressed by a cell comprising a polynucleotide encoding amino acids 197 to 764 of SEQ ID NO:2 operably associated with a regulatory sequence that controls gene expression. In still other embodiments, antibodies of the present invention bind a PA polypeptide expressed by a cell comprising a polynucleotide encoding amino acids 625 to 764 of SEQ ID NO:2 operably associated with a regulatory sequence that controls gene expression.

Antibodies of the present invention that may bind PA polypeptide fragments comprising or alternatively, consisting of, an amino acid sequence contained in SEQ ID NO:2. Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Antibodies of the present invention may bind polypeptide fragments, including, for example, fragments that comprise or alternatively, consist of from about amino acid residues: 1 to 29, 30 to 59, 60 to 89, 90 to 119, 120 to 149, 150 to 175, 176 to 196, 197 to 226, 227 to 256, 257 to 287, 288 to 312, 313 to 337, 338 to 362, 363 to 387, 388 to 412, 413 to 437, 438 to 462, 463 to 487, 488 to 516, 517 to 542, 543 to 569, 570 to 569, 570 to 596, 597 to 624, 625 to 652, 653 to 680, 681 to 708, 709 to 736, and/or 737 to 764 of SEQ ID NO:2. In this context "about" includes the particularly recited value, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Moreover, polypeptide fragments that antibodies of the invention may bind can be at least about 10, 20, 30, 40, 50, 60, 70, 86, 90, 100, 110, 120, 130, 140, 150, 175 or 200 amino acids in length. In this context "about" includes the particularly recited value, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes.

Preferably, antibodies of the present invention bind polypeptide fragments selected from the group: a polypeptide comprising or alternatively, consisting of, the full length PA polypeptide (amino acid residues 1 to 764 in SEQ ID NO:2); a polypeptide comprising or alternatively, consisting of, the secreted form of PA (amino acid residues 30 to 764 in SEQ ID NO:2); a polypeptide comprising or alternatively, consisting of, the PA20 fragment (amino acid residues from about 30 to about 196 in SEQ ID NO:2); a polypeptide comprising or alternatively, consisting of, the PA63 fragment (amino acid residues from about 197 to about 764 in SEQ ID NO:2); a polypeptide comprising or alternatively, consisting of, PA domain I (amino acid residues 30 to 287 of SEQ ID NO:2); a polypeptide comprising or alternatively, consisting of, PA domain II (amino acid residues 288 to 516 of SEQ ID NO:2); a polypeptide comprising or alternatively, consisting of, PA domain III (amino acid residues 517 to 624 of SEQ ID NO:2); a polypeptide comprising or alternatively, consisting of, PA domain IV (amino acid residues 625 to 764 of SEQ ID NO:2); a polypeptide comprising or alternatively, consisting of, fragment of the predicted mature PA polypeptide; and a polypeptide comprising, or alternatively, consisting of, one, two, three, four or more, epitope bearing portions of the PA receptor protein. In additional embodiments, the polypeptide fragments of the invention comprise, or alternatively, consist of, any combination of 1, 2, 3, 4, 5, 6, 7, or all 8 of the above members. The amino acid residues constituting these

domains may vary slightly (e.g., by about 1 to about 15 amino acid residues) depending on the criteria used to define each domain.

Domain I contains the proteolytic cleavage site. When the secreted form of PA is cleaved at this site, a 20 kilodalton fragment (PA20) is released from PA, generating the biologically active 63 kilodalton PA63 fragment. Thus, in specific embodiments antibodies of the invention bind an epitope at or near this cleavage site and prevent the cleavage of the secreted form of PA that results in the generation of PA20 and PA63. In specific embodiments, antibodies of the invention that prevent cleavage of PA into PA20 and PA63 may bind one or more PA peptides (as well as the native amino acid secreted form of the protein, PA83, see, e.g., Example 2) selected from the group consisting of: (a) amino acid residues 190 to 209 of SEQ ID NO:2; (b) amino acid residues 181 to 201 of SEQ ID NO:2; (c) amino acid residues 198 to 212 of SEQ ID NO:2; (d) amino acid residues 196 to 212 of SEQ ID NO:2; (e) amino acid residues 194 to 212 of SEQ ID NO:2; (f) amino acid residues 192 to 212 of SEQ ID NO:2; (g) amino acid residues 190 to 212 of SEQ ID NO:2; (h) amino acid residues 188 to 212 of SEQ ID NO:2; (i) amino acid residues 186 to 212 of SEQ ID NO:2; (j) amino acid residues 184 to 212 of SEQ ID NO:2; and (k) amino acid residues 181 to 195 of SEQ ID NO:2.

Domain IV of PA is important for interactions between PA and its receptor (e.g., ATR (SEQ ID NO:3) or CMG2 (SEQ ID NO:42)). Accordingly, in preferred embodiments, antibodies of the present invention bind PA polypeptide fragments comprising, or alternatively consisting of amino acid residues 625 to 764 of SEQ ID NO:2. In preferred embodiments, the antibodies of the invention that bind all or a portion of domain IV of PA prevent PA from binding to ATR and/or CMG2. In other preferred embodiments, the antibodies of the invention that bind all or a portion of domain IV of PA protect cells from death induced by anthrax toxins.

Antibodies of the invention may also bind fragments comprising, or alternatively, consisting of structural or functional attributes of PA. Such fragments include amino acid residues that comprise alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet-forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, surface forming regions, and high antigenic index regions (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) of complete (i.e., full-length) PA. Certain preferred regions are those set out in Table 2 and include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence depicted in (SEQ ID NO:2), such preferred regions include: Garnier-Robson predicted alpha-regions, beta-regions, turn-regions, and coil-regions; Chou-Fasman predicted alpha-regions, beta-regions, and turn-regions; Kyte-Doolittle predicted hydrophilic regions; Eisenberg alpha and beta amphipathic regions; Emini surface-forming regions; and Jameson-Wolf high antigenic index regions, as predicted using the default parameters of these computer programs.

The data representing the structural or functional attributes of PA set forth in Table 2, as described above, was generated using the various modules and algorithms of the DNA*STAR set on default parameters. Column I represents the results of a Garnier-Robson analysis of alpha helical regions; Column II represents the results of a Chou-Fasman analysis of alpha helical regions; Column III represents the results of a Garnier

Robson analysis of beta sheet regions; Column IV represents the results of a Chou-Fasman analysis of beta sheet regions; Column V represents the results of a Garnier Robson analysis of turn regions; Column VI represents the results of a Chou-Fasman analysis of turn regions; Column VII represents the results of a Garnier Robson analysis of coil regions; Column VIII represents a Kyte-Doolittle hydrophilicity plot; Column IX represents the results of an Eisenberg analysis of alpha amphipathic regions; Column X represents the results of an Eisenberg analysis of beta amphipathic regions; Column XI represents the results of a Karplus-Schultz analysis of flexible regions; Column XII represents the Jameson-Wolf antigenic index score; and Column XIII represents the Emini surface probability plot.

In a preferred embodiment, the data presented in columns VIII, XII, and XIII of Table 2 can be used to determine regions of PA which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, XII, and/or XIII by choosing

values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

The above-mentioned preferred regions set out in Table 2 include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence set out in SEQ ID NO:2. As set out in Table 2, such preferred regions include Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and turn-regions, Kyte-Doolittle hydrophilic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schultz flexible regions, Jameson-Wolf regions of high antigenic index and Emini surface-forming regions. Among preferred polypeptide fragments bound by one or more antibodies of the invention are those that comprise regions of PA that combine several structural features, such as several (e.g., 1, 2, 3, or 4) of the same or different region features set out above and in Table 2.

TABLE 2

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII
Met	1	A	A	1.59	.	.	.	0.75	2.90
Lys	2	A	A	1.12	.	.	.	0.75	4.54
Lys	3	A	A	.	B	.	.	.	0.70	.	.	.	0.75	2.64
Arg	4	A	A	.	B	.	.	.	0.20	.	.	.	0.75	2.20
Lys	5	A	A	.	B	.	.	.	0.38	.	.	F	0.75	0.77
Val	6	.	A	B	B	.	.	.	0.17	.	.	.	0.60	0.60
Leu	7	.	A	B	B	.	.	.	-0.48	.	.	.	-0.30	0.25
Ile	8	.	A	B	B	.	.	.	-1.11	.	.	.	-0.60	0.12
Pro	9	.	A	B	B	.	.	.	-2.03	.	.	.	-0.60	0.17
Leu	10	.	A	B	B	.	.	.	-2.38	.	.	.	-0.60	0.17
Met	11	A	A	.	B	.	.	.	-1.83	.	.	.	-0.60	0.32
Ala	12	A	A	.	B	.	.	.	-1.91	.	.	.	-0.60	0.30
Leu	13	A	A	.	B	.	.	.	-1.83	.	.	.	-0.60	0.26
Ser	14	.	A	B	B	.	.	.	-2.48	.	.	.	-0.60	0.21
Thr	15	.	.	B	B	.	.	.	-1.97	.	.	.	-0.60	0.16
Ile	16	.	.	B	B	.	.	.	-1.67	.	.	.	-0.60	0.25
Leu	17	.	.	B	B	.	.	.	-1.39	.	.	.	-0.60	0.25
Val	18	.	.	B	B	.	.	.	-0.92	.	.	.	-0.60	0.25
Ser	19	.	.	B	B	.	.	.	-0.62	.	*	F	-0.36	0.36
Ser	20	T	C	.	-1.12	.	*	F	0.33	0.70
Thr	21	T	C	.	-0.23	.	*	F	0.42	0.78
Gly	22	T	C	.	-0.28	.	*	F	1.56	1.01
Asn	23	T	C	.	-0.31	.	*	F	0.90	0.56
Leu	24	A	A	-0.01	.	.	.	0.06	0.27
Glu	25	A	A	-0.30	.	.	.	-0.03	0.47
Val	26	A	A	0.01	.	*	.	-0.12	0.30
Ile	27	A	A	-0.50	.	*	.	0.39	0.63
Gln	28	A	A	-0.46	*	*	.	0.30	0.27
Ala	29	A	A	0.36	*	*	.	0.30	0.72
Glu	30	A	A	0.36	*	*	.	0.45	1.79
Val	31	A	A	1.21	*	*	F	0.90	1.79
Lys	32	A	A	2.21	*	*	F	0.90	2.84
Gln	33	A	A	1.40	*	*	F	0.90	3.21
Glu	34	A	A	1.18	*	*	F	0.90	3.57
Asn	35	A	A	1.18	*	*	F	0.90	1.47
Arg	36	A	A	2.03	*	*	F	0.60	1.37
Leu	37	A	A	1.69	*	.	F	0.90	1.37
Leu	38	A	A	1.69	*	.	F	0.94	1.14
Asn	39	T	C	.	1.39	*	.	F	2.18	1.01
Glu	40	A	.	.	.	T	.	.	1.09	*	.	F	2.02	1.64
Ser	41	T	C	.	0.68	*	.	F	2.86	2.66
Glu	42	T	T	.	1.49	.	.	F	3.40	2.22
Ser	43	T	T	.	1.96	.	.	F	3.06	2.22
Ser	44	T	T	.	1.14	.	.	F	2.72	1.64
Ser	45	T	T	.	0.33	.	.	F	1.93	0.78
Gln	46	.	.	B	.	T	.	.	0.29	.	.	F	0.59	0.48
Gly	47	.	.	B	B	.	.	.	0.04	.	.	F	-0.45	0.35
Leu	48	.	.	B	B	.	.	.	0.10	.	.	F	-0.45	0.41
Leu	49	.	.	B	B	.	.	.	-0.30	.	.	.	-0.60	0.37
Gly	50	.	.	B	B	.	.	.	-0.30	.	.	.	-0.60	0.33
Tyr	51	.	.	B	B	.	.	.	-0.30	.	.	.	-0.60	0.53
Tyr	52	.	.	B	B	.	.	.	-0.77	.	.	.	-0.45	1.08

TABLE 2-continued

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII
Phe	53	.	.	B	B	.	.	.	0.04	.	.	.	-0.60	0.90
Ser	54	.	.	B	0.16	.	*	.	-0.40	0.92
Asp	55	.	A	B	0.50	.	*	.	-0.60	0.51
Leu	56	.	A	B	0.16	.	*	.	-0.45	1.02
Asn	57	.	A	.	.	T	.	.	0.19	.	*	.	0.10	0.77
Phe	58	.	A	.	.	T	.	.	0.29	.	*	.	0.10	0.71
Gln	59	A	A	-0.27	.	*	.	-0.60	0.85
Ala	60	.	A	B	B	.	.	.	-1.12	.	*	.	-0.60	0.39
Pro	61	.	A	B	B	.	.	.	-0.62	.	*	.	-0.60	0.34
Met	62	.	A	B	B	.	.	.	-0.92	.	*	.	-0.60	0.28
Val	63	.	A	B	B	.	.	.	-0.52	.	.	.	-0.60	0.37
Val	64	.	.	B	B	.	.	.	-0.83	.	.	.	-0.60	0.32
Thr	65	.	.	B	B	.	.	.	-0.56	.	.	F	-0.20	0.47
Ser	66	.	.	B	B	.	.	.	-0.69	.	.	F	0.05	0.92
Ser	67	.	.	B	B	.	.	.	-0.09	.	.	F	0.75	1.22
Thr	68	.	.	B	.	.	T	.	-0.04	.	.	F	2.00	1.42
Thr	69	T	T	.	0.51	.	*	F	2.50	0.87
Gly	70	T	T	.	-0.07	.	*	F	2.25	0.87
Asp	71	.	.	B	.	.	T	.	0.02	.	*	F	1.00	0.42
Leu	72	.	.	B	0.02	.	*	F	0.55	0.45
Ser	73	.	.	B	0.03	.	*	F	0.90	0.61
Ile	74	.	.	B	.	.	T	.	0.34	.	*	F	0.85	0.49
Pro	75	.	.	B	.	.	T	.	-0.12	.	*	F	1.00	1.04
Ser	76	T	C	-0.12	.	.	F	1.05	0.64
Ser	77	T	C	0.69	*	.	F	1.20	1.57
Glu	78	A	A	0.10	*	.	F	0.90	1.64
Leu	79	.	A	B	0.78	*	.	F	0.71	0.86
Glu	80	.	A	.	.	T	.	.	0.69	*	.	F	1.37	0.99
Asn	81	.	A	C	0.99	.	.	F	1.43	0.76
Ile	82	C	1.29	*	.	F	2.04	1.61
Pro	83	C	1.29	.	.	F	2.60	1.49
Ser	84	T	T	.	1.86	*	.	F	2.44	1.61
Glu	85	A	T	.	1.16	*	.	F	1.18	3.59
Asn	86	A	T	.	1.16	.	.	F	0.92	2.01
Gln	87	T	T	.	1.74	*	.	F	1.06	2.60
Tyr	88	.	.	B	B	.	.	.	1.37	*	.	.	-0.15	2.01
Phe	89	.	.	B	B	.	.	.	0.78	.	.	.	-0.45	1.26
Gln	90	.	.	B	B	.	.	.	0.49	.	.	.	-0.60	0.51
Ser	91	.	.	B	B	.	.	.	0.19	*	.	.	-0.60	0.34
Ala	92	.	.	B	B	.	.	.	-0.16	*	.	.	-0.60	0.53
Ile	93	.	.	B	B	.	.	.	-0.61	.	.	.	-0.60	0.30
Trp	94	A	T	.	-0.80	*	.	.	-0.20	0.20
Ser	95	A	T	.	-0.76	*	.	.	-0.20	0.14
Gly	96	A	T	.	-1.31	*	.	.	-0.20	0.39
Phe	97	A	T	.	-0.68	*	.	.	-0.20	0.27
Ile	98	.	A	B	B	.	.	.	0.26	*	.	.	0.30	0.41
Lys	99	A	A	.	B	.	.	.	0.24	.	.	.	0.60	0.83
Val	100	.	A	.	B	.	.	C	0.54	.	*	F	1.70	1.28
Lys	101	.	A	.	B	.	.	C	0.89	.	*	F	2.00	3.05
Lys	102	.	A	C	1.34	.	.	F	2.30	2.64
Ser	103	T	C	1.92	.	*	F	3.00	5.57
Asp	104	A	T	.	1.18	.	.	F	2.50	4.02
Glu	105	A	T	.	1.44	.	.	F	2.20	1.74
Tyr	106	.	.	B	.	.	T	.	1.09	.	.	.	1.45	1.31
Thr	107	A	.	.	B	.	.	.	0.74	.	.	.	0.15	1.13
Phe	108	A	.	.	B	.	.	.	0.46	.	.	.	-0.30	0.88
Ala	109	A	.	.	B	.	.	.	0.46	.	.	.	-0.60	0.57
Thr	110	A	.	.	B	.	.	.	0.46	.	.	F	0.06	0.65
Ser	111	A	T	.	0.67	*	.	F	0.82	1.22
Ala	112	A	T	.	0.12	*	.	F	1.63	1.64
Asp	113	A	T	.	0.51	*	.	F	1.69	0.84
Asn	114	T	C	0.50	*	.	F	2.10	0.91
His	115	.	.	.	B	.	.	C	0.52	*	.	.	0.74	0.89
Val	116	.	.	B	B	.	.	.	-0.03	*	.	.	0.03	0.56
Thr	117	.	.	B	B	.	.	.	0.56	*	.	.	-0.18	0.26
Met	118	.	.	B	B	.	.	.	0.56	.	.	.	-0.39	0.32
Trp	119	A	.	.	B	.	.	.	0.56	.	.	.	-0.30	0.71
Val	120	A	T	.	0.59	.	.	.	0.10	0.86
Asp	121	A	T	.	0.59	.	.	F	1.00	1.50
Asp	122	A	T	.	0.01	.	.	F	1.00	1.06
Gln	123	A	T	.	0.61	*	.	F	1.15	1.00
Glu	124	A	A	.	B	.	.	.	0.94	*	.	F	0.75	0.96
Val	125	A	A	.	B	.	.	.	1.21	.	.	.	0.75	1.15
Ile	126	A	A	.	B	.	.	.	0.91	*	.	.	0.30	0.67
Asn	127	A	A	.	B	.	.	.	0.91	*	.	.	0.60	0.52
Lys	128	A	A	0.61	*	.	F	0.60	1.13
Ala	129	A	A	0.61	*	.	F	1.50	2.15

TABLE 2-continued

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII
Ser	130	.	A	C	1.51	*	.	F	2.30	2.15
Asn	131	T	C	1.51	.	*	F	3.00	2.15
Ser	132	T	C	1.62	.	*	F	2.40	1.49
Asn	133	A	T	.	0.77	.	*	F	2.20	2.18
Lys	134	.	.	B	.	.	T	.	1.36	.	*	F	1.60	1.12
Ile	135	.	A	B	1.70	.	*	F	1.20	1.45
Arg	136	.	A	B	1.36	.	*	.	0.75	1.80
Leu	137	.	A	B	1.77	.	*	F	0.75	0.89
Glu	138	A	A	0.96	.	*	F	0.90	2.49
Lys	139	A	A	0.67	.	*	F	0.90	1.05
Gly	140	A	.	.	B	.	.	.	1.56	*	.	F	0.60	1.99
Arg	141	A	.	.	B	.	.	.	0.56	.	.	F	0.90	1.99
Leu	142	A	.	.	B	.	.	.	1.41	.	*	.	0.30	0.70
Tyr	143	A	.	.	B	.	.	.	0.52	.	*	.	0.45	1.41
Gln	144	.	.	B	B	.	.	.	0.48	.	*	.	-0.30	0.50
Ile	145	.	.	B	B	.	.	.	0.58	.	*	.	-0.45	1.06
Lys	146	.	.	B	B	.	.	.	0.47	*	.	.	-0.45	1.06
Ile	147	.	.	B	B	.	.	.	1.39	*	.	.	-0.15	1.06
Gln	148	.	.	B	B	.	.	.	1.63	.	*	.	0.45	2.96
Tyr	149	.	.	B	1.63	.	*	.	0.95	2.56
Gln	150	.	.	B	2.31	.	*	F	0.80	5.88
Arg	151	T	.	.	1.96	.	.	F	1.84	5.25
Glu	152	C	2.84	.	.	F	1.98	4.83
Asn	153	T	C	2.89	.	.	F	2.52	4.83
Pro	154	T	C	2.79	.	.	F	2.86	4.93
Thr	155	T	T	.	1.98	.	.	F	3.40	2.82
Glu	156	A	T	.	1.87	.	*	F	2.66	1.45
Lys	157	A	A	1.17	.	*	F	1.92	1.56
Gly	158	A	A	1.21	.	*	F	1.43	0.94
Leu	159	A	A	0.61	.	.	.	1.09	1.08
Asp	160	A	A	0.68	.	.	.	0.30	0.45
Phe	161	.	.	B	B	.	.	.	0.39	.	*	.	-0.30	0.71
Lys	162	.	.	B	B	.	.	.	0.03	.	*	.	-0.60	0.90
Leu	163	.	.	B	B	.	.	.	0.38	.	*	.	-0.60	0.78
Tyr	164	.	.	B	B	.	.	.	0.89	.	*	.	-0.45	1.50
Trp	165	A	.	.	B	.	.	.	0.89	.	*	.	0.15	1.01
Thr	166	A	.	.	B	.	.	.	1.59	.	*	F	0.30	2.11
Asp	167	A	.	.	B	.	.	.	1.59	.	.	F	0.90	2.17
Ser	168	A	T	.	2.44	.	.	F	2.20	4.12
Gln	169	T	C	2.69	.	.	F	3.00	5.71
Asn	170	T	C	2.12	.	.	F	2.70	5.93
Lys	171	T	C	1.54	.	.	F	2.40	3.28
Lys	172	.	A	B	1.24	.	.	F	1.50	1.33
Glu	173	.	A	B	1.24	.	.	F	1.20	1.11
Val	174	.	A	B	1.24	.	.	F	1.03	0.74
Ile	175	.	A	B	1.24	.	.	F	1.31	0.62
Ser	176	.	.	B	.	.	T	.	0.39	.	.	F	1.99	0.58
Ser	177	.	.	B	.	.	T	.	0.34	.	.	F	1.37	0.64
Asp	178	T	T	.	-0.47	.	.	F	2.80	1.58
Asn	179	T	C	0.18	.	.	F	2.17	0.97
Leu	180	A	A	1.07	.	.	.	1.29	1.12
Gln	181	A	A	0.56	.	.	.	1.01	1.16
Leu	182	A	A	0.90	.	.	.	-0.02	0.60
Pro	183	A	A	0.90	.	.	F	0.60	1.45
Glu	184	A	A	0.94	.	*	F	0.60	1.45
Leu	185	A	A	1.46	.	.	F	0.90	3.51
Lys	186	A	A	1.16	*	.	F	0.90	3.04
Gln	187	A	A	1.97	*	.	F	1.24	2.35
Lys	188	A	A	1.88	.	*	F	1.58	4.59
Ser	189	A	T	.	1.99	*	.	F	2.32	3.07
Ser	190	A	T	.	2.84	.	*	F	2.66	3.48
Asn	191	T	T	.	2.84	.	.	F	3.40	3.48
Ser	192	T	T	.	2.96	.	.	F	3.06	5.19
Arg	193	T	.	.	2.61	.	.	F	2.52	7.58
Lys	194	T	.	.	2.60	.	.	F	2.18	6.32
Lys	195	T	.	.	2.60	.	.	F	1.84	6.80
Arg	196	.	.	B	2.01	.	.	F	1.10	4.65
Ser	197	.	.	B	1.97	.	.	F	1.10	2.35
Thr	198	.	.	B	1.64	.	.	F	1.10	1.16
Ser	199	T	T	.	1.29	.	.	F	1.25	0.92
Ala	200	T	C	0.39	*	.	F	0.71	0.99
Gly	201	T	C	0.07	*	.	F	0.97	0.51
Pro	202	.	.	B	.	.	T	.	0.37	*	.	F	1.03	0.59
Thr	203	.	.	B	0.79	.	.	F	1.69	0.97
Val	204	.	.	B	.	.	T	.	1.09	.	.	F	2.60	1.92
Pro	205	.	.	B	.	.	T	.	1.68	*	.	F	2.34	2.07
Asp	206	.	.	B	.	.	T	.	2.02	*	.	F	2.42	2.31

TABLE 2-continued

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII
Arg	207	.	.	B	.	.	T	.	1.89	*	.	F	2.50	5.20
Asp	208	T	T	.	1.31	*	.	F	2.98	3.33
Asn	209	T	T	.	1.96	*	.	F	3.06	1.40
Asp	210	T	T	.	2.17	*	.	F	3.40	1.10
Gly	211	T	C	1.87	*	.	F	2.86	1.10
Ile	212	T	C	0.94	*	.	F	2.37	0.92
Pro	213	T	C	0.94	*	.	F	1.73	0.45
Asp	214	T	C	0.09	*	*	F	1.39	0.79
Ser	215	.	.	B	.	.	T	.	0.09	*	*	F	0.85	0.84
Leu	216	.	A	B	0.09	.	*	.	0.60	0.94
Glu	217	.	A	B	0.73	.	*	.	0.60	0.56
Val	218	A	A	0.63	.	.	.	0.30	0.65
Glu	219	A	A	-0.22	.	.	.	0.45	1.14
Gly	220	A	A	0.08	.	*	.	0.30	0.49
Tyr	221	A	.	.	B	.	.	.	0.03	.	*	.	0.45	1.10
Thr	222	A	.	.	B	.	.	.	0.08	.	*	.	0.30	0.47
Val	223	A	.	.	B	.	.	.	0.93	.	*	.	0.56	0.95
Asp	224	A	.	.	B	.	.	.	0.98	.	.	.	0.82	0.98
Val	225	A	1.43	.	*	F	1.88	1.36
Lys	226	A	1.37	.	*	F	2.14	3.58
Asn	227	.	.	B	.	.	T	.	0.98	.	*	F	2.60	3.09
Lys	228	.	.	B	.	.	T	.	1.02	.	*	F	2.34	3.61
Arg	229	.	.	B	.	.	T	.	0.72	.	.	F	2.08	1.49
Thr	230	.	.	B	.	.	T	.	1.37	*	.	F	1.52	1.24
Phe	231	.	.	B	1.03	*	.	F	0.91	0.96
Leu	232	.	.	B	0.14	.	.	.	-0.40	0.51
Ser	233	T	C	-0.20	.	.	.	0.00	0.25
Pro	234	T	T	.	-0.31	*	.	.	0.20	0.39
Trp	235	T	T	.	-0.89	*	.	.	0.20	0.75
Ile	236	A	T	.	-0.22	*	.	.	-0.20	0.39
Ser	237	A	.	.	B	.	.	.	0.59	*	.	.	-0.60	0.35
Asn	238	A	A	.	B	.	.	.	0.93	.	.	.	-0.60	0.57
Ile	239	A	A	.	B	.	.	.	1.19	.	.	.	0.45	1.63
His	240	A	A	.	B	.	.	.	1.13	.	.	.	0.75	2.44
Glu	241	A	A	1.21	.	.	F	0.90	1.50
Lys	242	A	A	1.20	.	.	F	0.90	1.76
Lys	243	A	A	1.24	.	.	F	0.90	1.87
Gly	244	A	A	1.89	.	*	F	0.90	2.16
Leu	245	A	1.97	*	.	F	1.44	1.69
Thr	246	A	T	.	1.67	*	.	F	1.98	1.69
Lys	247	.	.	B	.	.	T	.	1.32	*	.	F	2.02	2.29
Tyr	248	.	.	B	.	.	T	.	1.07	*	*	F	2.36	3.72
Lys	249	T	T	.	1.41	*	.	F	3.40	3.99
Ser	250	C	2.27	*	.	F	2.66	3.45
Ser	251	T	C	2.29	*	*	F	2.52	4.41
Pro	252	T	C	1.94	*	*	F	2.18	2.32
Glu	253	T	T	.	1.88	*	.	F	2.04	2.32
Lys	254	T	T	.	1.24	*	.	F	1.40	2.50
Trp	255	T	.	.	1.24	.	.	F	1.20	1.63
Ser	256	.	.	B	1.54	.	.	F	0.80	1.26
Thr	257	.	.	B	1.54	*	.	F	1.10	1.05
Ala	258	T	.	.	1.30	*	.	F	1.20	1.55
Ser	259	C	0.96	*	.	F	1.90	1.81
Asp	260	T	C	1.24	*	.	F	2.40	1.68
Pro	261	T	C	0.84	*	.	F	3.00	2.78
Tyr	262	T	T	.	1.16	*	.	F	2.60	1.80
Ser	263	T	C	.	1.79	*	.	F	2.40	1.86
Asp	264	A	A	1.23	*	.	F	1.50	2.41
Phe	265	A	A	0.92	*	.	F	0.90	1.14
Glu	266	A	A	0.79	*	*	F	0.90	1.23
Lys	267	A	A	1.14	*	*	F	0.75	0.73
Val	268	A	A	0.56	*	*	F	0.90	1.65
Thr	269	A	.	.	B	.	.	.	0.56	*	*	F	0.75	0.67
Gly	270	A	.	.	B	.	.	.	1.30	*	*	F	0.75	0.56
Arg	271	A	.	.	B	.	.	.	1.30	*	*	F	0.90	1.50
Ile	272	.	.	B	B	.	.	.	0.40	*	*	F	1.20	1.67
Asp	273	T	T	.	0.96	*	*	F	2.30	1.25
Lys	274	T	C	1.06	*	*	F	2.25	0.86
Asn	275	T	C	1.40	*	*	F	2.40	1.89
Val	276	T	C	0.70	*	*	F	3.00	1.96
Ser	277	T	C	1.70	*	*	F	2.55	0.99
Pro	278	T	C	1.67	*	*	F	2.40	1.21
Glu	279	A	T	.	1.41	*	*	F	1.90	2.21
Ala	280	A	T	.	0.60	*	*	F	1.60	2.56
Arg	281	A	0.60	.	*	.	0.65	1.36
His	282	.	.	B	B	.	.	.	0.31	.	*	.	0.30	0.58
Pro	283	.	.	B	B	.	.	.	-0.07	.	*	.	-0.30	0.58

TABLE 2-continued

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII
Leu	284	A	.	.	B	.	.	.	-0.31	.	*	.	-0.30	0.30
Val	285	A	.	.	B	.	.	.	0.07	*	*	.	-0.60	0.35
Ala	286	A	.	.	B	.	.	.	-0.93	*	.	.	-0.60	0.35
Ala	287	.	.	B	B	.	.	.	-1.76	.	.	.	-0.60	0.29
Tyr	288	.	.	B	B	.	.	.	-1.58	.	.	.	-0.60	0.29
Pro	289	.	.	B	B	.	.	.	-1.62	.	.	.	-0.60	0.40
Ile	290	.	.	B	B	.	.	.	-0.77	.	.	.	-0.60	0.29
Val	291	.	.	B	B	.	.	.	-0.78	.	*	.	-0.60	0.31
His	292	.	.	B	B	.	.	.	-0.19	.	*	.	-0.60	0.20
Val	293	.	.	B	B	.	.	.	0.06	.	.	.	-0.30	0.49
Asp	294	A	.	.	B	.	.	.	-0.62	.	.	.	0.45	1.07
Met	295	A	A	-0.62	.	.	.	0.30	0.55
Glu	296	A	A	-0.58	.	*	.	-0.30	0.52
Asn	297	A	A	-0.84	.	.	.	-0.30	0.26
Ile	298	A	A	0.06	.	.	.	-0.60	0.35
Ile	299	A	A	0.06	.	.	.	0.30	0.40
Leu	300	A	A	0.66	.	.	.	0.04	0.40
Ser	302	A	A	0.66	.	.	F	1.23	0.99
Lys	302	A	A	0.66	.	.	F	1.92	2.36
Asn	303	T	C	1.24	.	.	F	2.86	4.95
Glu	304	T	T	.	1.82	*	.	F	3.40	4.95
Asp	305	T	T	.	2.63	*	.	F	3.06	3.57
Gln	306	T	T	.	2.93	.	.	F	2.72	3.85
Ser	307	T	.	.	2.58	.	.	F	2.18	3.57
Thr	308	.	.	B	2.58	.	.	F	1.42	3.09
Gln	309	T	.	.	2.28	.	.	F	1.76	2.98
Asn	310	T	C	.	2.28	.	.	F	2.04	2.98
Thr	311	T	C	.	1.97	*	*	F	2.32	3.57
Asp	312	T	T	.	2.38	.	*	F	2.80	2.98
Ser	313	.	.	B	.	.	T	.	2.38	*	.	F	2.42	3.62
Gln	314	.	.	B	B	.	.	.	1.49	*	.	F	1.74	3.62
Thr	315	.	.	B	B	.	.	.	1.19	*	*	F	1.46	1.52
Arg	316	.	.	B	B	.	.	.	1.54	*	.	F	0.88	1.52
Thr	317	.	.	B	B	.	.	.	1.54	*	.	F	0.90	1.76
Ile	318	.	.	B	B	.	.	.	1.53	*	.	F	0.90	1.96
Ser	319	.	.	B	.	.	T	.	1.23	*	.	F	1.60	1.44
Lys	320	T	T	.	1.23	*	.	F	2.00	1.34
Asn	321	T	C	.	0.82	*	.	F	2.10	2.76
Thr	322	T	C	.	1.24	.	.	F	2.40	2.76
Ser	323	T	C	.	1.82	.	.	F	3.00	2.70
Thr	324	T	C	.	2.09	.	.	F	2.40	2.42
Ser	325	T	C	.	1.73	.	.	F	2.36	2.29
Arg	326	T	C	.	1.43	.	.	F	2.32	2.46
Thr	327	C	.	1.74	.	.	F	2.08	2.29
His	328	T	C	.	1.19	*	.	F	2.54	2.95
Thr	329	.	.	B	.	T	.	.	1.47	.	.	F	2.60	1.12
Ser	330	.	.	B	.	T	.	.	1.42	.	*	F	2.04	1.06
Glu	331	.	.	B	.	T	.	.	1.31	.	*	F	1.63	0.77
Val	332	C	.	1.03	.	*	F	1.37	0.86
His	333	T	C	.	1.07	.	*	F	1.31	0.64
Gly	334	T	C	.	0.52	.	*	.	1.20	0.64
Asn	335	A	.	.	.	T	.	.	0.79	.	*	.	0.10	0.64
Ala	336	A	.	.	.	T	.	.	0.20	.	*	.	0.70	0.64
Glu	337	A	A	0.76	.	*	.	0.30	0.66
Val	338	A	A	0.09	.	*	.	0.30	0.55
His	339	A	A	-0.27	.	*	.	-0.30	0.47
Ala	340	A	A	-0.27	.	*	.	-0.60	0.24
Ser	341	.	A	B	-0.57	*	*	.	-0.60	0.53
Phe	342	.	A	B	-0.91	*	.	.	-0.60	0.27
Phe	343	.	A	B	-0.40	.	.	.	-0.60	0.27
Asp	344	T	T	.	-0.67	*	*	.	0.20	0.20
Ile	345	T	T	.	-0.93	*	*	.	0.20	0.30
Gly	346	T	T	.	-0.93	*	*	F	0.65	0.26
Gly	347	T	C	.	-0.82	*	*	F	1.05	0.21
Ser	348	C	.	-0.47	*	*	F	-0.05	0.30
Val	349	.	.	B	-1.17	*	*	F	0.05	0.30
Ser	350	.	.	B	.	T	.	.	-0.58	*	*	.	-0.20	0.26
Ala	351	.	.	B	.	T	.	.	-0.23	.	.	.	-0.08	0.26
Gly	352	.	.	B	.	T	.	.	-0.19	.	.	.	0.04	0.57
Phe	353	.	.	B	.	T	.	.	0.11	.	.	F	0.61	0.57
Ser	354	C	.	0.67	.	.	F	0.73	0.92
Asn	355	T	C	.	0.67	.	.	F	1.20	1.24
Ser	356	T	C	.	0.94	.	.	F	1.08	1.91
Asn	357	T	C	.	0.43	.	.	F	1.56	2.06
Ser	358	T	C	.	0.54	.	.	F	0.69	0.95
Ser	359	.	.	.	B	.	C	.	-0.04	.	.	F	0.17	0.72
Thr	360	.	.	B	B	.	.	.	-0.04	.	.	F	-0.45	0.31

TABLE 2-continued

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII
Val	361	.	.	B	B	.	.	.	0.22	.	.	.	-0.30	0.39
Ala	362	.	.	B	B	.	.	.	-0.08	.	*	.	-0.30	0.40
Ile	363	.	.	B	B	.	.	.	-0.59	.	*	.	-0.30	0.37
Asp	364	.	.	B	B	.	.	.	-0.59	.	*	.	-0.30	0.41
His	365	.	.	B	-1.09	.	*	.	-0.10	0.54
Ser	366	A	A	-0.82	.	*	.	-0.30	0.64
Leu	367	.	A	B	-0.58	.	*	.	-0.30	0.38
Ser	368	.	A	C	0.31	.	*	.	-0.40	0.28
Leu	369	.	A	C	0.42	.	.	.	-0.10	0.36
Ala	370	A	A	0.14	*	.	.	0.30	0.86
Gly	371	A	A	0.16	*	.	F	0.75	0.93
Glu	372	A	A	0.38	*	.	F	0.00	1.18
Arg	373	A	A	0.68	.	.	F	0.60	1.18
Thr	374	A	A	1.18	*	.	F	0.90	2.06
Trp	375	A	A	1.17	*	.	.	0.75	1.72
Ala	376	A	A	1.17	*	.	.	0.30	0.87
Glu	377	A	A	0.36	.	.	.	-0.60	0.60
Thr	378	A	A	0.24	.	.	.	-0.60	0.47
Met	379	A	A	0.24	.	.	.	-0.30	0.74
Gly	380	.	A	C	-0.06	.	.	.	-0.10	0.62
Leu	381	.	A	C	0.53	.	.	.	-0.40	0.43
Asn	382	A	A	0.22	.	.	F	-0.15	0.73
Thr	383	A	A	-0.06	*	.	F	0.60	1.07
Ala	384	A	A	0.66	.	*	F	0.00	1.31
Asp	385	A	A	0.19	.	*	F	0.90	1.59
Thr	386	A	A	1.00	.	*	F	0.45	0.91
Ala	387	A	A	0.41	*	*	F	0.60	1.45
Arg	388	A	A	0.72	*	*	.	0.30	0.88
Leu	389	A	A	0.42	.	*	.	0.30	0.98
Asn	390	A	T	.	0.53	*	*	.	0.10	0.68
Ala	391	.	.	B	.	.	T	.	0.60	*	*	.	0.70	0.68
Asn	392	.	.	B	.	.	T	.	0.33	*	*	.	-0.05	1.29
Ile	393	.	.	B	.	.	T	.	0.22	*	*	.	0.10	0.59
Arg	394	.	.	B	B	.	.	.	0.72	*	*	.	-0.30	0.95
Tyr	395	.	.	B	B	.	.	.	0.38	*	*	.	-0.30	0.85
Val	396	.	.	B	B	.	.	.	0.66	*	*	.	-0.15	1.20
Asn	397	.	.	B	.	.	T	.	0.07	*	*	F	0.25	0.88
Thr	398	.	.	B	.	.	T	.	0.74	*	*	F	-0.05	0.57
Gly	399	T	T	.	-0.26	*	.	F	0.80	1.19
Thr	400	.	.	B	.	.	T	.	-0.26	*	.	F	-0.05	0.52
Ala	401	.	.	B	B	.	.	.	0.60	*	.	F	-0.45	0.56
Pro	402	.	.	B	B	.	.	.	-0.26	*	.	.	-0.60	0.91
Ile	403	.	.	B	B	.	.	.	-0.76	*	.	.	-0.60	0.47
Tyr	404	.	.	B	B	.	.	.	-0.62	*	.	.	-0.60	0.38
Asn	405	.	.	B	B	.	.	.	-0.62	.	.	.	-0.60	0.38
Val	406	.	.	B	B	.	.	.	-0.34	.	.	.	-0.60	0.79
Leu	407	.	.	B	B	.	.	.	-0.43	.	.	.	-0.60	0.73
Pro	408	.	.	B	.	.	T	.	-0.36	.	.	F	-0.05	0.61
Thr	409	.	.	B	.	.	T	.	-0.97	.	.	F	-0.05	0.67
Thr	410	.	.	B	.	.	T	.	-1.78	.	.	F	-0.05	0.61
Ser	411	.	.	B	.	.	T	.	-1.27	.	.	F	-0.05	0.32
Leu	412	.	.	B	B	.	.	.	-0.41	.	.	.	-0.60	0.22
Val	413	.	.	B	B	.	.	.	-0.20	.	.	.	-0.30	0.31
Leu	414	.	.	B	B	.	.	.	0.11	.	.	.	-0.30	0.37
Gly	415	T	T	.	0.11	.	.	F	0.65	0.77
Lys	416	A	T	.	-0.40	.	.	F	0.40	1.50
Asn	417	A	T	.	-0.18	.	.	F	0.40	1.50
Gln	418	A	T	.	0.37	.	.	F	1.00	1.54
Thr	419	A	.	.	B	.	.	.	0.29	.	*	F	0.60	1.11
Leu	420	A	.	.	B	.	.	.	0.68	.	*	F	-0.45	0.48
Ala	421	A	.	.	B	.	.	.	0.04	.	*	.	-0.30	0.56
Thr	422	A	.	.	B	.	.	.	0.09	.	*	.	-0.30	0.39
Ile	423	A	.	.	B	.	.	.	0.09	.	*	.	0.30	0.95
Lys	424	A	.	.	B	.	.	.	0.40	.	*	F	0.90	1.62
Ala	425	A	A	1.21	.	*	F	0.90	1.81
Lys	426	A	A	0.99	.	*	F	0.90	4.47
Glu	427	A	A	1.00	*	*	F	0.90	1.84
Asn	428	A	A	1.89	*	*	F	0.90	2.44
Gln	429	A	A	.	B	.	.	.	0.96	*	.	F	0.90	2.12
Leu	430	A	A	.	B	.	.	.	0.73	.	.	F	0.45	0.86
Ser	431	.	A	B	B	.	.	.	0.10	.	.	F	-0.45	0.44
Gln	432	.	A	B	B	.	.	.	-0.11	.	.	.	-0.60	0.26
Ile	433	.	A	B	B	.	.	.	-0.11	*	.	.	-0.60	0.48
Leu	434	.	A	B	B	.	.	.	-0.11	.	.	.	-0.60	0.58
Ala	435	.	.	B	.	.	T	.	0.46	.	.	.	-0.20	0.54
Pro	436	.	.	B	.	.	T	.	0.51	.	.	F	0.10	1.20
Asn	437	T	T	.	0.30	.	.	F	0.50	2.27

TABLE 2-continued

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII
Asn	438	T	T	.	0.89	.	.	F	0.50	3.48
Tyr	439	T	.	.	1.74	.	.	F	0.30	3.02
Tyr	440	.	.	B	.	.	T	.	2.33	.	.	F	0.40	3.75
Pro	441	T	T	.	1.73	.	.	F	0.80	3.75
Ser	442	T	T	.	1.14	.	.	F	0.50	1.97
Lys	443	.	.	B	.	.	T	.	0.93	.	.	F	0.40	1.27
Asn	444	.	A	B	0.29	*	.	F	0.60	1.27
Leu	445	.	A	B	-0.06	.	.	.	-0.30	0.67
Ala	446	.	A	B	-0.66	*	.	.	-0.30	0.34
Pro	447	.	A	B	-0.36	*	.	.	-0.60	0.17
Ile	448	.	A	B	-0.99	*	*	.	-0.60	0.34
Ala	449	A	A	-0.99	*	.	.	-0.60	0.34
Leu	450	.	A	B	-0.18	*	*	.	-0.60	0.38
Asn	451	.	A	B	0.41	*	.	.	0.04	0.90
Ala	452	A	A	-0.08	*	*	F	1.58	1.48
Gln	453	A	A	0.51	*	*	F	1.62	1.56
Asp	454	T	T	.	0.80	*	*	F	3.06	1.30
Asp	455	T	T	.	1.30	.	*	F	3.40	1.72
Phe	456	T	T	.	1.09	.	*	F	3.06	1.43
Ser	457	.	.	B	.	.	T	.	0.79	.	.	F	2.32	1.33
Ser	458	.	.	B	B	.	.	.	0.48	.	.	F	0.53	0.56
Thr	459	.	.	.	B	.	.	C	-0.12	.	.	F	0.09	0.93
Pro	460	.	.	.	B	.	.	C	-0.12	.	.	F	-0.25	0.69
Ile	461	.	.	.	B	T	.	.	0.33	.	*	F	-0.05	0.82
Thr	462	.	.	B	B	.	.	.	0.63	.	.	.	-0.60	0.89
Met	463	.	.	B	B	.	.	.	0.93	.	.	.	-0.60	0.93
Asn	464	.	.	B	.	.	T	.	0.54	*	.	.	-0.05	2.30
Tyr	465	.	.	B	.	.	T	.	-0.06	*	.	.	-0.05	1.38
Asn	466	T	C	0.83	*	*	.	0.15	1.15
Gln	467	A	T	.	0.33	.	*	.	-0.05	1.24
Phe	468	A	A	0.93	.	.	.	-0.60	0.65
Leu	469	A	A	0.98	*	.	.	0.30	0.70
Glu	470	A	A	0.91	.	.	.	0.30	0.81
Leu	471	A	A	0.96	.	.	.	0.45	1.35
Glu	472	A	A	0.96	.	.	F	0.90	3.27
Lys	473	A	A	0.84	.	*	F	0.90	3.27
Thr	474	A	A	1.77	.	*	F	0.90	3.27
Lys	475	A	A	0.96	.	*	F	0.90	3.70
Gln	476	A	A	1.77	.	*	F	0.90	1.53
Leu	477	A	A	1.46	.	*	.	0.98	1.77
Arg	478	.	A	B	1.41	.	*	.	1.21	1.27
Leu	479	.	A	B	1.72	*	*	.	1.44	1.23
Asp	480	.	.	B	.	.	T	.	0.82	*	*	F	2.22	2.58
Thr	481	.	.	B	.	.	T	.	0.58	.	*	F	2.30	0.98
Asp	482	.	.	B	.	.	T	.	1.04	.	*	F	1.92	1.86
Gln	483	.	.	B	.	.	T	.	0.93	.	*	F	1.69	1.10
Val	484	.	.	B	B	.	.	.	0.86	.	.	.	0.31	1.23
Tyr	485	.	.	B	B	.	.	.	0.27	*	.	.	-0.07	0.52
Gly	486	.	.	B	B	.	.	.	0.27	*	.	.	-0.60	0.30
Asn	487	.	.	B	B	.	.	.	0.02	.	.	.	-0.60	0.58
Ile	488	.	.	B	B	.	.	.	0.02	.	*	.	-0.60	0.58
Ala	489	.	.	B	B	.	.	.	0.18	*	.	.	-0.60	0.95
Thr	490	.	.	B	B	.	.	.	0.42	.	.	.	-0.60	0.51
Tyr	491	.	.	B	0.77	*	.	.	-0.25	1.26
Asn	492	.	.	B	0.42	*	.	.	0.39	2.01
Phe	493	.	.	B	.	.	T	.	1.42	.	.	.	0.93	1.38
Glu	494	T	T	.	1.16	.	*	F	2.42	1.72
Asn	495	T	T	.	1.58	.	*	F	2.61	0.80
Gly	496	T	T	.	0.97	.	*	F	3.40	1.80
Arg	497	.	.	B	B	.	.	.	0.97	.	*	F	2.11	0.77
Val	498	.	.	B	B	.	.	.	1.36	.	*	F	1.77	0.80
Arg	499	.	.	B	B	.	.	.	1.01	.	*	.	1.55	1.17
Val	500	.	.	B	B	.	.	.	0.71	.	*	F	1.33	0.59
Asp	501	.	.	B	B	.	.	.	1.06	.	*	F	0.96	1.07
Thr	502	C	.	0.66	.	*	F	1.63	0.87
Gly	503	T	C	1.21	.	*	F	1.20	1.24
Ser	504	T	C	1.10	.	*	F	0.93	0.99
Asn	505	T	C	1.10	*	.	F	0.96	1.19
Trp	506	T	C	0.29	*	.	F	0.69	0.89
Ser	507	C	0.39	*	.	F	0.07	0.55
Glu	508	.	.	B	0.73	*	.	.	-0.40	0.53
Val	509	.	.	B	B	.	.	.	0.14	*	*	.	-0.60	0.87
Leu	510	.	.	B	B	.	.	.	0.14	*	.	F	-0.15	0.46
Pro	511	.	.	.	B	.	.	C	0.43	*	.	F	0.05	0.46
Gln	512	.	.	.	B	.	.	C	0.42	*	.	F	0.20	1.06
Ile	513	A	.	.	B	.	.	.	0.11	*	.	F	0.00	1.86
Gln	514	A	.	.	B	.	.	.	0.38	*	*	F	0.60	1.74

TABLE 2-continued

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII
Glu	515	A	.	.	B	.	.	.	1.30	*	*	F	0.60	1.01
Thr	516	.	.	B	B	.	.	.	0.62	*	.	F	0.60	2.83
Thr	517	.	.	B	B	.	.	.	-0.27	*	*	F	0.60	1.15
Ala	518	.	.	B	B	.	.	.	-0.08	*	*	.	0.30	0.46
Arg	519	.	.	B	B	.	.	.	-0.08	*	*	.	-0.60	0.28
Ile	520	.	.	B	B	.	.	.	-0.42	*	*	.	-0.60	0.31
Ile	521	.	.	B	B	.	.	.	-0.07	*	*	.	-0.36	0.30
Phe	522	.	.	B	B	.	.	.	0.24	*	*	.	0.78	0.31
Asn	523	.	.	.	R	T	.	.	0.02	*	*	F	1.57	0.74
Gly	524	T	T	.	-0.09	*	*	F	2.21	0.87
Lys	525	T	C	-0.01	.	.	F	2.40	1.62
Asp	526	T	C	0.02	.	.	F	2.01	0.83
Leu	527	T	C	0.72	*	*	F	1.77	0.62
Asn	528	A	A	0.83	*	.	.	1.08	0.54
Leu	529	A	A	1.29	*	.	.	0.84	0.63
Val	530	A	A	0.36	*	.	.	0.75	1.50
Glu	531	A	A	-0.23	*	*	.	0.60	0.65
Arg	532	A	A	-0.01	*	.	.	0.30	0.80
Arg	533	A	A	-0.87	*	.	.	0.75	1.09
Ile	534	.	A	B	-0.06	*	.	.	0.60	0.47
Ala	535	.	A	B	0.59	*	.	.	0.30	0.38
Ala	536	.	A	B	0.29	.	.	.	-0.30	0.30
Val	537	.	A	B	0.18	*	.	.	-0.30	0.58
Asn	538	T	C	-0.14	.	.	F	1.65	0.96
Pro	539	T	C	-0.07	.	.	F	2.10	1.46
Ser	540	T	C	0.52	*	.	F	2.40	1.63
Asp	541	T	C	0.80	.	.	F	3.00	1.75
Pro	542	C	1.34	.	.	F	2.50	1.64
Leu	543	.	.	B	1.39	.	.	F	2.00	1.76
Glu	544	.	.	B	1.39	.	.	F	1.70	2.11
Thr	545	A	1.69	.	.	F	1.10	2.11
Thr	546	A	1.09	.	.	F	1.10	4.27
Lys	547	A	T	.	0.99	.	*	F	1.30	2.44
Pro	548	A	T	.	0.99	.	*	F	1.00	2.44
Asp	549	A	T	.	1.03	.	*	F	1.00	1.39
Met	550	A	T	.	1.34	*	*	F	1.30	1.39
Thr	551	A	A	1.07	*	*	.	0.75	1.56
Leu	552	A	A	0.21	*	*	.	0.60	0.94
Lys	553	A	A	0.47	*	*	F	0.45	0.79
Glu	554	A	A	-0.42	*	*	F	0.90	1.09
Ala	555	A	A	-0.41	*	*	.	0.30	0.93
Leu	556	A	A	-0.80	*	*	.	0.60	0.47
Lys	557	A	A	-0.33	*	*	.	-0.30	0.23
Ile	558	A	A	-1.08	*	*	.	-0.60	0.23
Ala	559	A	A	-1.08	*	*	.	-0.60	0.24
Phe	560	.	A	B	-0.49	*	*	.	-0.60	0.19
Gly	561	.	A	B	0.11	.	*	.	-0.32	0.48
Phe	562	.	.	B	0.07	.	*	.	0.46	0.73
Asn	563	C	0.61	.	.	F	1.24	1.36
Glu	564	T	C	1.20	.	.	F	2.32	1.36
Pro	565	T	T	.	1.09	.	*	F	2.80	2.53
Asn	566	T	T	.	1.43	.	*	F	2.52	1.30
Gly	567	T	T	.	1.89	.	*	F	2.24	1.30
Asn	568	C	1.89	.	*	F	0.66	1.31
Leu	569	.	.	B	1.54	*	.	.	0.23	1.41
Gln	570	.	.	B	1.80	.	*	.	0.15	1.41
Tyr	571	.	.	B	.	.	T	.	1.80	*	*	.	0.85	1.76
Gln	572	.	.	B	.	.	T	.	1.26	*	*	F	1.80	3.56
Gly	573	.	.	B	.	.	T	.	0.94	*	*	F	2.00	1.44
Lys	574	.	.	B	.	.	T	.	1.76	*	*	F	1.80	1.33
Asp	575	.	A	B	1.06	*	*	F	1.50	1.33
Ile	576	.	A	B	1.30	.	*	F	1.30	1.16
Thr	577	.	A	B	0.60	*	*	F	0.95	0.97
Glu	578	.	A	B	0.94	*	*	.	0.30	0.50
Phe	579	.	A	B	0.20	*	*	.	-0.15	1.15
Asp	580	.	A	.	.	T	.	.	0.20	*	*	.	0.10	0.69
Phe	581	.	A	.	.	T	.	.	1.09	*	*	.	0.70	0.67
Asn	582	T	T	.	1.40	.	*	.	0.65	1.34
Phe	583	T	T	.	1.09	.	*	F	1.40	1.38
Asp	584	A	T	.	1.49	.	*	F	0.40	2.31
Gln	585	A	T	.	1.49	.	*	F	1.28	1.92
Gln	586	T	.	.	2.19	*	*	F	1.76	3.85
Thr	587	C	1.30	*	*	F	2.14	3.70
Ser	588	T	C	2.04	*	*	F	1.72	1.50
Gln	589	T	T	.	2.04	*	*	F	2.80	1.73
Asn	590	T	T	.	2.04	*	*	F	2.52	1.93
Ile	591	T	C	1.23	*	*	F	2.04	2.49

TABLE 2-continued

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII
Lys	592	.	A	C	0.96	*	.	F	1.36	1.19
Asn	593	.	A	B	1.26	*	.	F	0.13	0.75
Gln	594	.	A	B	0.44	*	.	F	0.60	1.84
Leu	595	.	A	B	0.44	*	.	.	0.30	0.76
Ala	596	.	A	B	0.74	*	.	.	-0.30	0.76
Glu	597	A	A	0.39	.	.	.	-0.30	0.44
Leu	598	A	A	0.39	.	.	.	-0.30	0.78
Asn	599	A	A	-0.50	.	.	.	0.45	1.23
Ala	600	A	.	.	B	.	.	.	0.07	.	.	.	-0.30	0.50
Thr	601	A	.	.	B	.	.	.	0.34	.	.	.	-0.60	0.95
Asn	602	A	.	.	B	.	.	.	-0.51	.	.	.	-0.60	0.85
Ile	603	.	.	B	B	.	.	.	-0.51	.	.	.	-0.60	0.63
Tyr	604	.	.	B	B	.	.	.	-0.51	*	.	.	-0.60	0.36
Thr	605	.	A	B	B	.	.	.	0.12	*	.	.	-0.60	0.37
Val	606	.	A	B	B	.	.	.	-0.46	*	.	.	-0.15	1.06
Leu	607	A	A	.	B	.	.	.	-0.41	*	.	.	-0.30	0.47
Asp	608	A	A	.	B	.	.	.	-0.33	*	.	F	0.45	0.66
Lys	609	A	A	.	B	.	.	.	-0.09	*	.	F	0.45	0.73
Ile	610	A	A	.	B	.	.	.	-0.37	*	.	F	0.90	1.42
Lys	611	A	A	.	B	.	.	.	0.53	*	.	F	0.75	0.86
Leu	612	A	A	0.74	.	.	F	0.75	0.86
Asn	613	A	A	0.74	.	.	.	0.45	1.22
Ala	614	A	A	-0.19	.	.	.	0.30	0.98
Lys	615	A	A	-0.11	.	.	.	-0.30	0.83
Met	616	A	.	.	B	.	.	.	-1.04	*	.	.	-0.30	0.43
Asn	617	A	.	.	B	.	.	.	-0.12	*	.	.	-0.60	0.30
Ile	618	A	.	.	B	.	.	.	-0.12	.	.	.	-0.30	0.29
Leu	619	A	.	.	B	.	.	.	0.51	.	.	.	-0.30	0.49
Ile	620	A	.	.	B	.	.	.	0.58	.	.	.	0.60	0.61
Arg	621	A	.	.	B	.	.	.	0.48	*	.	.	0.75	1.70
Asp	622	A	.	.	B	.	.	.	0.44	*	.	F	0.90	1.78
Lys	623	.	A	B	1.09	*	.	F	0.90	3.46
Arg	624	.	A	B	1.90	*	.	.	1.03	2.77
Phe	625	.	A	B	2.90	.	.	.	1.31	2.77
His	626	.	A	.	.	T	.	.	2.79	.	.	.	1.99	2.71
Tyr	627	.	A	.	.	T	.	.	2.79	.	.	.	2.27	2.23
Asp	628	T	T	.	1.86	*	.	F	2.80	4.13
Arg	629	T	T	.	1.16	.	.	F	2.52	2.13
Asn	630	T	T	.	1.00	.	.	F	2.24	1.37
Asn	631	T	T	.	0.69	.	.	.	1.66	0.61
Ile	632	.	.	B	B	.	.	.	0.34	*	.	.	-0.02	0.31
Ala	633	.	.	B	B	.	.	.	0.34	*	.	.	-0.60	0.19
Val	634	.	.	B	B	.	.	.	0.23	*	.	.	-0.30	0.20
Gly	635	A	.	.	B	.	.	.	-0.07	*	.	.	0.30	0.50
Ala	636	A	A	-0.92	.	.	F	0.75	0.66
Asp	637	A	A	-0.89	*	.	F	0.45	0.66
Glu	638	A	A	.	B	.	.	.	-0.26	*	.	F	0.45	0.49
Ser	639	A	A	.	B	.	.	.	0.60	*	.	F	0.75	0.98
Val	640	A	A	.	B	.	.	.	0.36	*	.	F	0.90	1.02
Val	641	A	A	.	B	.	.	.	0.91	*	.	.	0.60	0.59
Lys	642	A	A	.	B	.	.	.	1.02	*	.	.	0.30	0.60
Glu	643	A	A	1.02	*	.	.	0.75	1.59
Ala	644	A	A	0.47	*	.	.	0.75	3.70
His	645	A	A	0.43	*	.	.	0.75	1.37
Arg	646	A	A	.	B	.	.	.	1.29	*	.	.	0.60	0.56
Glu	647	A	A	.	B	.	.	.	0.94	*	.	.	0.54	0.89
Val	648	A	A	.	B	.	.	.	0.64	*	.	.	0.78	0.87
Ile	649	A	A	.	B	.	.	.	0.92	*	.	.	1.02	0.60
Asn	650	T	C	0.96	*	.	F	2.01	0.50
Ser	651	T	C	0.50	*	.	F	2.40	1.16
Ser	652	T	C	-0.31	*	.	F	2.16	1.64
Thr	653	T	C	-0.27	.	.	F	1.77	0.84
Glu	654	A	A	-0.19	.	.	F	0.33	0.52
Gly	655	A	A	-0.19	.	.	F	0.09	0.32
Leu	656	A	A	-0.78	*	.	.	-0.30	0.35
Leu	657	A	A	-0.48	*	.	.	-0.60	0.14
Leu	658	A	A	-0.12	*	.	.	-0.60	0.24
Asn	659	A	A	-0.12	*	.	.	-0.30	0.59
Ile	660	A	A	-0.67	*	.	F	0.90	1.19
Asp	661	A	T	.	0.26	*	.	F	1.30	1.01
Lys	662	A	T	.	1.11	*	.	F	1.30	1.23
Asp	663	A	T	.	1.03	*	.	F	1.30	3.51
Ile	664	A	T	.	0.22	*	.	F	1.30	1.47
Arg	665	.	.	B	B	.	.	.	0.81	*	.	F	0.75	0.61
Lys	666	.	.	B	B	.	.	.	0.47	*	.	F	0.75	0.49
Ile	667	.	.	B	B	.	.	.	0.18	*	.	.	0.30	0.69
Leu	668	.	.	B	.	.	T	.	-0.71	*	.	.	0.70	0.55

TABLE 2-continued

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII
Ser	669	.	.	B	.	.	T	.	-0.68	*	.	.	-0.20	0.19
Gly	670	.	.	B	.	.	T	.	-0.79	*	.	.	-0.20	0.20
Tyr	671	.	.	B	.	.	T	.	-1.72	*	.	.	-0.20	0.43
Ile	672	.	.	B	B	.	.	.	-0.83	*	.	.	-0.60	0.22
Val	673	.	.	B	B	.	.	.	-0.02	*	.	.	-0.30	0.39
Glu	674	.	.	B	B	.	.	.	-0.03	.	.	.	0.30	0.42
Ile	675	.	.	B	B	.	.	.	0.31	.	.	.	0.30	0.86
Glu	676	A	.	.	B	.	.	.	0.21	.	.	F	0.90	2.01
Asp	677	A	T	.	0.29	.	.	F	1.30	1.15
Thr	678	A	T	.	1.19	.	*	F	1.30	1.35
Glu	679	A	T	.	1.19	.	.	F	1.30	1.56
Gly	680	A	T	.	1.22	*	.	F	1.30	1.62
Leu	681	A	A	0.33	*	.	F	0.75	0.83
Lys	682	A	A	0.33	*	.	F	0.75	0.34
Glu	683	A	A	0.64	*	*	.	0.30	0.55
Val	684	A	A	0.76	*	*	.	0.75	1.11
Ile	685	A	A	0.86	*	*	.	0.75	1.09
Asn	686	A	T	.	1.67	*	*	.	1.00	0.98
Asp	687	A	T	.	1.02	*	*	.	1.15	2.21
Arg	688	A	T	.	0.21	*	.	.	1.15	3.12
Tyr	689	A	T	.	1.07	.	.	.	1.15	1.60
Asp	690	.	.	B	1.07	.	*	.	0.95	1.54
Met	691	.	.	B	B	.	.	.	0.77	.	.	.	-0.30	0.55
Leu	692	.	.	B	B	.	.	.	0.47	.	.	.	-0.60	0.47
Asn	693	.	.	B	B	.	.	.	-0.46	.	.	.	-0.30	0.38
Ile	694	.	.	B	B	.	.	.	-0.10	.	.	.	-0.60	0.32
Ser	695	.	.	B	B	.	.	.	-0.10	.	.	F	0.19	0.75
Ser	696	.	.	B	B	.	.	.	0.50	.	.	F	1.13	0.81
Leu	697	.	.	B	B	.	.	.	0.97	*	*	F	1.62	1.92
Arg	698	A	T	.	1.01	*	*	F	2.66	1.42
Gln	699	T	T	.	1.59	*	*	F	3.40	2.12
Asp	700	T	T	.	1.19	*	*	F	3.06	3.71
Gly	701	T	T	.	0.60	*	*	F	2.72	1.64
Lys	702	.	.	B	1.41	*	*	F	1.33	0.66
Thr	703	.	.	B	0.60	*	*	F	1.29	0.66
Phe	704	.	A	B	0.64	*	*	.	-0.30	0.58
Ile	705	.	A	B	0.69	*	*	.	0.30	0.58
Asp	706	A	A	0.79	*	*	.	0.64	0.80
Phe	707	A	A	0.74	*	*	.	0.53	1.46
Lys	708	A	A	1.06	*	.	F	1.62	3.34
Lys	709	.	A	.	.	T	.	.	1.80	*	.	F	2.66	3.34
Tyr	710	T	T	.	1.88	*	*	F	3.40	7.72
Asn	711	T	T	.	1.67	*	*	F	3.06	3.18
Asp	712	T	T	.	1.56	*	*	F	2.72	2.46
Lys	713	.	.	B	.	.	T	.	1.27	*	*	F	1.68	1.29
Leu	714	.	.	B	B	.	.	.	0.33	*	.	.	0.79	1.26
Pro	715	.	.	B	B	.	.	.	0.28	*	.	.	-0.30	0.53
Leu	716	.	.	B	B	.	.	.	0.28	*	.	.	-0.60	0.35
Tyr	717	.	.	B	B	.	.	.	0.07	*	.	.	-0.60	0.69
Ile	718	.	.	B	B	.	.	.	0.02	.	*	.	-0.60	0.69
Ser	719	.	.	B	B	.	.	.	0.59	*	.	.	-0.45	1.35
Asn	720	.	.	B	.	.	T	.	0.84	*	.	F	0.10	1.35
Pro	721	T	T	.	0.80	.	*	F	0.80	3.85
Asn	722	T	T	.	1.04	.	*	F	0.80	2.13
Tyr	723	T	T	.	1.08	.	*	F	0.80	2.13
Lys	724	.	.	B	B	.	.	.	1.13	.	.	.	-0.15	1.02
Val	725	.	.	B	B	.	.	.	0.54	.	.	.	-0.60	1.00
Asn	726	.	.	B	B	.	.	.	-0.10	.	*	.	-0.60	0.64
Val	727	.	.	B	B	.	.	.	-0.41	.	*	.	-0.60	0.24
Tyr	728	.	.	B	B	.	.	.	-0.12	.	*	.	-0.60	0.46
Ala	729	.	.	B	B	.	.	.	-0.17	.	*	.	-0.60	0.58
Val	730	A	.	.	B	.	.	.	0.69	.	*	.	-0.15	1.35
Thr	731	A	.	.	B	.	.	.	0.38	.	.	F	0.60	1.38
Lys	732	.	.	B	B	.	.	.	0.34	.	.	F	0.60	1.97
Glu	733	.	.	B	B	.	.	.	-0.30	*	.	F	0.60	1.86
Asn	734	.	.	B	B	.	.	.	0.29	*	.	F	0.45	0.91
Thr	735	.	.	B	B	.	.	.	0.93	.	.	F	0.45	0.73
Ile	736	.	.	B	B	.	.	.	0.94	.	.	.	-0.30	0.65
Ile	737	.	.	B	B	.	.	.	0.90	.	.	.	-0.26	0.54
Asn	738	.	.	B	.	.	T	.	0.90	*	.	F	0.93	0.65
Pro	739	T	C	0.56	*	.	F	2.22	1.49
Ser	740	T	C	0.87	*	.	F	2.56	2.11
Glu	741	T	T	.	1.44	*	.	F	3.40	2.19
Asn	742	T	T	.	2.03	.	*	F	3.06	2.04
Gly	743	T	T	.	1.72	.	.	F	2.72	2.04
Asp	744	T	T	.	1.93	.	.	F	2.38	1.70
Thr	745	T	C	1.89	*	.	F	1.54	1.70

TABLE 2-continued

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII
Ser	746	T	C	1.00	*	.	F	1.20	1.70
Thr	747	A	T	.	1.04	*	.	F	0.85	0.71
Asn	748	A	T	.	1.43	*	.	F	0.85	0.99
Gly	749	A	T	.	0.54	*	.	F	1.30	1.48
Ile	750	A	.	.	B	.	.	.	0.04	*	.	F	0.45	0.72
Lys	751	.	.	B	B	.	.	.	-0.54	*	.	F	0.45	0.37
Lys	752	.	.	B	B	.	.	.	-0.93	*	.	F	-0.15	0.26
Ile	753	.	.	B	B	.	.	.	-1.23	*	.	.	-0.60	0.32
Leu	754	.	.	B	B	.	.	.	-0.84	*	.	.	-0.30	0.22
Ile	755	.	.	B	B	.	.	.	0.09	*	.	.	-0.30	0.22
Phe	756	.	.	B	B	.	.	.	-0.30	*	.	.	0.04	0.62
Ser	757	T	C	-0.59	*	.	F	1.73	0.74
Lys	758	T	T	.	0.30	*	.	F	1.82	1.65
Lys	759	T	C	0.22	*	.	F	2.86	3.30
Gly	760	T	T	.	0.77	*	.	F	3.40	1.73
Tyr	761	T	.	.	1.08	*	.	F	2.71	0.85
Glu	762	.	.	B	0.99	*	.	.	1.52	0.55
Ile	763	.	.	B	0.56	*	.	.	0.58	0.71
Gly	764	.	.	B	0.12	.	.	.	0.24	0.58

In another aspect, the invention provides an antibody that binds a peptide or polypeptide comprising an epitope-bearing portion of a polypeptide described herein. The epitope of this polypeptide portion is an immunogenic or antigenic epitope of a polypeptide of the invention.

As to the selection of peptides or polypeptides bearing an antigenic epitope (i.e., that contain a region of a protein molecule to which an antibody can bind), it is well known in that art that relatively short synthetic peptides that mimic part of a protein sequence are routinely capable of eliciting an antiserum that reacts with the partially mimicked protein. See, for instance, Sutcliffe, J. G., Shinnick, T. M., Green, N. and Learner, R. A. (1983) Antibodies that react with predetermined sites on proteins. *Science* 219:660-666. Peptides capable of eliciting protein-reactive sera are frequently represented in the primary sequence of a protein, can be characterized by a set of simple chemical rules, and are confined neither to immunodominant regions of intact proteins (i.e., immunogenic epitopes) nor to the amino or carboxyl terminals.

Antigenic epitope-bearing peptides and polypeptides are therefore useful to raise antibodies, including monoclonal antibodies, that bind to a PA polypeptide of the invention. See, for instance, Wilson et al., *Cell* 37:767-778 (1984) at 777. Antigenic epitope-bearing peptides and polypeptides preferably contain a sequence of at least seven, more preferably at least nine and most preferably between at least about 15 to about 30 amino acids contained within the amino acid sequence of SEQ ID NO:2.

Antibodies of the invention may bind one or more antigenic PA polypeptides or peptides including, but not limited to: a polypeptide comprising amino acid residues from about 39 to about 45 of SEQ ID NO:2; a polypeptide comprising amino acid residues from about 129 to about 134 of SEQ ID NO:2; a polypeptide comprising amino acid residues from about 151 to about 157 of SEQ ID NO:2; a polypeptide comprising amino acid residues from about 168 to about 172 of SEQ ID NO:2; a polypeptide comprising amino acid residues from about 189 to about 195 of SEQ ID NO:2; a polypeptide comprising amino acid residues from about 203 to about 213 of SEQ ID NO:2; a polypeptide comprising amino acid residues from about 225 to about 230 of SEQ ID NO:2; a polypeptide comprising amino acid residues from about 246 to about 253 of SEQ ID NO:2; a polypeptide comprising amino acid residues from about 259 to about 264

of SEQ ID NO:2; a polypeptide comprising amino acid residues from about 273 to about 280 of SEQ ID NO:2; a polypeptide comprising amino acid residues from about 302 to about 307 of SEQ ID NO:2; a polypeptide comprising amino acid residues from about 309 to about 314 of SEQ ID NO:2; a polypeptide comprising amino acid residues from about 319 to about 331 of SEQ ID NO:2; a polypeptide comprising amino acid residues from about 452 to about 457 of SEQ ID NO:2; a polypeptide comprising amino acid residues from about 480 to about 483 of SEQ ID NO:2; a polypeptide comprising amino acid residues from about 494 to about 498 of SEQ ID NO:2; a polypeptide comprising amino acid residues from about 523 to about 527 of SEQ ID NO:2; a polypeptide comprising amino acid residues from about 538 to about 544 of SEQ ID NO:2; a polypeptide comprising amino acid residues from about 564 to about 567 of SEQ ID NO:2; a polypeptide comprising amino acid residues from about 572 to about 575 of SEQ ID NO:2; a polypeptide comprising amino acid residues from about 587 to about 591 of SEQ ID NO:2; a polypeptide comprising amino acid residues from about 626 to about 631 of SEQ ID NO:2; a polypeptide comprising amino acid residues from about 650 to about 653 of SEQ ID NO:2; a polypeptide comprising amino acid residues from about 697 to about 701 of SEQ ID NO:2; a polypeptide comprising amino acid residues from about 708 to about 713 of SEQ ID NO:2; a polypeptide comprising amino acid residues from about 739 to about 745 of SEQ ID NO:2; and/or a polypeptide comprising amino acid residues from about 757 to about 762 of SEQ ID NO:2. In this context "about" includes the particularly recited range, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either terminus or at both termini. Epitope-bearing PA peptides and polypeptides may be produced by any conventional means. Houghten, R. A., "General method for the rapid solid-phase synthesis of large numbers of peptides: specificity of antigen-antibody interaction at the level of individual amino acids," *Proc. Natl. Acad. Sci. USA* 82:5131-5135 (1985). This "Simultaneous Multiple Peptide Synthesis (SMPS)" process is further described in U.S. Pat. No. 4,631,211 to Houghten et al. (1986).

As one of skill in the art will appreciate, PA polypeptides and the epitope-bearing fragments thereof described herein can be combined with parts of the constant domain of immunoglobulins (IgG), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased

half-life in vivo. This has been shown, e.g., for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins (EPA 394,827; Traunecker et al., *Nature* 331:84-86 (1988)). Fusion proteins that have a disulfide-linked dimeric structure due to the IgG part can also be more efficient in binding and neutralizing other molecules than the monomeric PA protein or protein fragment alone (Fountoulakis et al., *J Biochem* 270:3958-3964 (1995)). Thus, antibodies of the invention may bind the PA moiety of fusion proteins that comprise all or a portion of a PA polypeptide.

Recombinant DNA technology known to those skilled in the art can be used to create novel mutant proteins or "muteins" including single or multiple amino acid substitutions, deletions, additions or fusion proteins. Such modified polypeptides can show, e.g., enhanced activity or increased stability. In addition, they may be purified in higher yields and show better solubility than the corresponding natural polypeptide, at least under certain purification and storage conditions. Antibodies of the present invention may also bind such modified PA polypeptides or PA polypeptide fragments or variants.

For instance, for many proteins, it is known in the art that one or more amino acids may be deleted from the N-terminus or C-terminus without substantial loss of biological function, or loss of the ability to be bound by a specific antibody. For instance, Ron et al., *J. Biol. Chem.*, 268:2984-2988 (1993) reported modified KGF proteins that had heparin binding activity even if 3, 8, or 27 amino-terminal amino acid residues were missing.

However, even if deletion of one or more amino acids from the N-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind EF or LF may still be retained. For example, the ability of shortened PA polypeptides to induce and/or bind to antibodies which recognize the complete or mature forms of the PA polypeptides generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a PA polypeptide with a large number of deleted N-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six PA amino acid residues may often evoke an immune response.

Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the PA amino acid sequence of SEQ ID NO:2 up to the serine residue at position number 463. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues n¹-764 of SEQ ID NO:2, where n¹ is an integer from 31 to 759 corresponding to the position of the amino acid residue in SEQ ID NO:2.

More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues of V-31 to G-764; K-32 to G-764; Q-33 to G-764; E-34 to G-764; N-35 to G-764; R-36 to G-764; L-37 to G-764; L-38 to G-764; N-39 to G-764; E-40 to G-764; S-41 to G-764; E-42 to G-764; S-43 to G-764; S-44 to G-764; S-45 to G-764; Q-46 to G-764; G-47 to G-764; L-48 to G-764; L-49 to G-764; G-50 to G-764; Y-51

to G-764; Y-52 to G-764; F-53 to G-764; S-54 to G-764; D-55 to G-764; L-56 to G-764; N-57 to G-764; F-58 to G-764; Q-59 to G-764; A-60 to G-764; P-61 to G-764; M-62 to G-764; V-63 to G-764; V-64 to G-764; T-65 to G-764; S-66 to G-764; S-67 to G-764; T-68 to G-764; T-69 to G-764; G-70 to G-764; D-71 to G-764; L-72 to G-764; S-73 to G-764; I-74 to G-764; P-75 to G-764; S-76 to G-764; S-77 to G-764; E-78 to G-764; L-79 to G-764; E-80 to G-764; N-81 to G-764; I-82 to G-764; P-83 to G-764; S-84 to G-764; E-85 to G-764; N-86 to G-764; Q-87 to G-764; Y-88 to G-764; F-89 to G-764; Q-90 to G-764; S-91 to G-764; A-92 to G-764; I-93 to G-764; W-94 to G-764; S-95 to G-764; G-96 to G-764; F-97 to G-764; I-98 to G-764; K-99 to G-764; V-100 to G-764; K-101 to G-764; K-102 to G-764; S-103 to G-764; D-104 to G-764; E-105 to G-764; Y-106 to G-764; T-107 to G-764; F-108 to G-764; A-109 to G-764; T-110 to G-764; S-111 to G-764; A-112 to G-764; D-113 to G-764; N-114 to G-764; H-115 to G-764; V-116 to G-764; T-117 to G-764; M-118 to G-764; W-119 to G-764; V-120 to G-764; D-121 to G-764; D-122 to G-764; Q-123 to G-764; E-124 to G-764; V-125 to G-764; I-126 to G-764; N-127 to G-764; K-128 to G-764; A-129 to G-764; S-130 to G-764; N-131 to G-764; S-132 to G-764; N-133 to G-764; K-134 to G-764; I-135 to G-764; R-136 to G-764; L-137 to G-764; E-138 to G-764; K-139 to G-764; G-140 to G-764; R-141 to G-764; L-142 to G-764; Y-143 to G-764; Q-144 to G-764; I-145 to G-764; K-146 to G-764; I-147 to G-764; Q-148 to G-764; Y-149 to G-764; Q-150 to G-764; R-151 to G-764; E-152 to G-764; N-153 to G-764; P-154 to G-764; T-155 to G-764; E-156 to G-764; K-157 to G-764; G-158 to G-764; L-159 to G-764; D-160 to G-764; F-161 to G-764; K-162 to G-764; L-163 to G-764; Y-164 to G-764; W-165 to G-764; T-166 to G-764; D-167 to G-764; S-168 to G-764; Q-169 to G-764; N-170 to G-764; K-171 to G-764; K-172 to G-764; E-173 to G-764; V-174 to G-764; I-175 to G-764; S-176 to G-764; S-177 to G-764; D-178 to G-764; N-179 to G-764; L-180 to G-764; Q-181 to G-764; L-182 to G-764; P-183 to G-764; E-184 to G-764; L-185 to G-764; K-186 to G-764; Q-187 to G-764; K-188 to G-764; S-189 to G-764; S-190 to G-764; N-191 to G-764; S-192 to G-764; R-193 to G-764; K-194 to G-764; K-195 to G-764; R-196 to G-764; S-197 to G-764; T-198 to G-764; S-199 to G-764; A-200 to G-764; G-201 to G-764; P-202 to G-764; T-203 to G-764; V-204 to G-764; P-205 to G-764; D-206 to G-764; R-207 to G-764; D-208 to G-764; N-209 to G-164; D-210 to G-764; G-211 to G-764; I-212 to G-764; P-213 to G-764; D-214 to G-764; S-215 to G-764; L-216 to G-764; E-217 to G-764; V-218 to G-764; E-219 to G-764; G-220 to G-764; Y-221 to G-764; T-222 to G-764; V-223 to G-764; D-224 to G-764; V-225 to G-764; K-226 to G-764; N-227 to G-764; K-228 to G-764; R-229 to G-764; T-230 to G-764; F-231 to G-764; L-232 to G-764; S-233 to G-764; P-234 to G-764; W-235 to G-764; I-236 to G-764; S-237 to G-764; N-238 to G-764; I-239 to G-764; H-240 to G-764; E-241 to G-764; K-242 to G-764; K-243 to G-764; G-244 to G-764; L-245 to G-764; T-246 to G-764; K-247 to G-764; Y-248 to G-764; K-249 to G-764; S-250 to G-764; S-251 to G-764; P-252 to G-764; E-253 to G-764; K-254 to G-764; W-255 to G-764; S-256 to G-764; T-257 to G-764; A-258 to G-764; S-259 to G-764; D-260 to G-764; P-261 to G-764; Y-262 to G-764; S-263 to G-764; D-264 to G-764; F-265 to G-764; E-266 to G-764; K-267 to G-764; V-268 to G-764; T-269 to G-764; G-270 to G-764; R-271 to G-764; I-272 to G-764; D-273 to G-764; K-274 to G-764; N-275 to G-764; V-276 to G-764; S-277 to G-764; P-278 to G-764; E-279 to G-764; A-280 to G-764; R-281 to G-764; H-282 to G-764; P-283 to G-764; L-284 to G-764; V-285 to G-764; A-286 to G-764; A-287 to G-764; Y-288 to G-764; P-289 to G-764; I-290 to G-764;

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G-764; S-757 to G-764; K-758 to G-764; and/or K-759 to G-764; of the amino acid sequence of SEQ ID NO:2.

As mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification of loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind EF or LF) may still be retained. For example, the ability of the shortened PA polypeptide to induce and/or bind to antibodies which recognize the complete or mature forms of the PA polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a PA polypeptide with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six PA amino acid residues may often evoke an immune response.

Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the PA polypeptide sequence of SEQ ID NO:2 up to the arginine residue at position number 36. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues 30-m¹ of SEQ ID NO:2, where m¹ is an integer from 36 to 763 corresponding to the position of the amino acid residue in SEQ ID NO:2.

More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues E-30 to I-763; E-30 to E-762; E-30 to Y-761; E-30 to G-760; E-30 to K-759; E-30 to K-758; E-30 to S-757; E-30 to F-756; E-30 to I-755; E-30 to L-754; E-30 to I-753; E-30 to K-752; E-30 to K-751; E-30 to I-750; E-30 to G-749; E-30 to N-748; E-30 to T-747; E-30 to S-746; E-30 to T-745; E-30 to D-744; E-30 to G-743; E-30 to N-742; E-30 to E-741; E-30 to S-740; E-30 to P-739; E-30 to N-738; E-30 to I-737; E-30 to I-736; E-30 to T-735; E-30 to N-734; E-30 to E-733; E-30 to K-732; E-30 to T-731; E-30 to V-730; E-30 to A-729; E-30 to Y-728; E-30 to V-727; E-30 to N-726; E-30 to V-725; E-30 to K-724; E-30 to Y-723; E-30 to N-722; E-30 to P-721; E-30 to N-720; E-30 to S-719; E-30 to I-718; E-30 to Y-717; E-30 to L-716; E-30 to P-715; E-30 to L-714; E-30 to K-713; E-30 to D-712; E-30 to N-711; E-30 to Y-710; E-30 to K-709; E-30 to K-708; E-30 to F-707; E-30 to D-706; E-30 to I-705; E-30 to F-704; E-30 to T-703; E-30 to K-702; E-30 to G-701; E-30 to D-700; E-30 to Q-699; E-30 to R-698; E-30 to L-697; E-30 to S-696; E-30 to S-695; E-30 to I-694; E-30 to N-693; E-30 to L-692; E-30 to M-691; E-30 to D-690; E-30 to Y-689; E-30 to R-688; E-30 to D-687; E-30 to N-686; E-30 to I-685; E-30 to V-684; E-30 to E-683; E-30 to K-682; E-30 to L-681; E-30 to G-680; E-30 to E-679; E-30 to T-678; E-30 to D-677; E-30 to E-676; E-30 to I-675; E-30 to E-674; E-30 to V-673; E-30 to I-672; E-30 to Y-671; E-30 to G-670; E-30 to S-669; E-30 to L-668; E-30 to I-667; E-30 to K-666; E-30 to R-665; E-30 to I-664; E-30 to D-663; E-30 to K-662; E-30 to D-661; E-30 to I-660; E-30 to N-659; E-30 to L-658; E-30 to L-657; E-30 to L-656; E-30 to G-655; E-30 to E-654; E-30 to T-653; E-30 to S-652; E-30 to S-651; E-30 to N-650; E-30 to I-649; E-30 to V-648; E-30 to E-647; E-30 to R-646; E-30 to H-645; E-30 to A-644; E-30 to E-643; E-30 to K-642; E-30 to V-641; E-30 to V-640; E-30 to S-639; E-30 to E-638; E-30 to D-637; E-30 to A-636; E-30 to G-635; E-30 to V-634; E-30 to A-633; E-30 to I-632; E-30 to N-631; E-30 to

N-630; E-30 to R-629; E-30 to D-628; E-30 to Y-627; E-30 to H-626; E-30 to F-625; E-30 to R-624; E-30 to K-623; E-30 to D-622; E-30 to R-621; E-30 to I-620; E-30 to L-619; E-30 to I-618; E-30 to N-617; E-30 to M-616; E-30 to K-615; E-30 to A-614; E-30 to N-613; E-30 to L-612; E-30 to K-611; E-30 to I-610; E-30 to K-609; E-30 to D-608; E-30 to L-607; E-30 to V-606; E-30 to T-605; E-30 to Y-604; E-30 to I-603; E-30 to N-602; E-30 to T-601; E-30 to A-600; E-30 to N-599; E-30 to L-598; E-30 to E-597; E-30 to A-596; E-30 to L-595; E-30 to Q-594; E-30 to N-593; E-30 to K-592; E-30 to I-591; E-30 to N-590; E-30 to Q-589; E-30 to S-588; E-30 to T-587; E-30 to Q-586; E-30 to Q-585; E-30 to D-584; E-30 to F-583; E-30 to N-582; E-30 to F-581; E-30 to D-580; E-30 to F-579; E-30 to E-578; E-30 to T-577; E-30 to I-576; E-30 to D-575; E-30 to K-574; E-30 to G-573; E-30 to Q-572; E-30 to Y-571; E-30 to Q-570; E-30 to L-569; E-30 to N-568; E-30 to G-567; E-30 to N-566; E-30 to P-565; E-30 to E-564; E-30 to N-563; E-30 to F-562; E-30 to G-561; E-30 to F-560; E-30 to A-559; E-30 to I-558; E-30 to K-557; E-30 to L-556; E-30 to A-555; E-30 to E-554; E-30 to K-553; E-30 to L-552; E-30 to T-551; E-30 to M-550; E-30 to D-549; E-30 to P-548; E-30 to K-547; E-30 to T-546; E-30 to T-545; E-30 to E-544; E-30 to L-543; E-30 to P-542; E-30 to D-541; E-30 to S-540; E-30 to P-539; E-30 to N-538; E-30 to V-537; E-30 to A-536; E-30 to A-535; E-30 to I-534; E-30 to R-533; E-30 to R-532; E-30 to E-531; E-30 to V-530; E-30 to L-529; E-30 to N-528; E-30 to L-527; E-30 to D-526; E-30 to K-525; E-30 to G-524; E-30 to N-523; E-30 to F-522; E-30 to I-521; E-30 to I-520; E-30 to R-519; E-30 to A-518; E-30 to T-517; E-30 to T-516; E-30 to E-515; E-30 to Q-514; E-30 to I-513; E-30 to Q-512; E-30 to P-511; E-30 to L-510; E-30 to V-509; E-30 to E-508; E-30 to S-507; E-30 to W-506; E-30 to N-505; E-30 to S-504; E-30 to G-503; E-30 to T-502; E-30 to D-501; E-30 to V-500; E-30 to R-499; E-30 to V-498; E-30 to R-497; E-30 to G-496; E-30 to N-495; E-30 to E-494; E-30 to F-493; E-30 to N-492; E-30 to Y-491; E-30 to T-490; E-30 to A-489; E-30 to I-488; E-30 to N-487; E-30 to G-486; E-30 to Y-485; E-30 to V-484; E-30 to Q-483; E-30 to D-482; E-30 to T-481; E-30 to D-480; E-30 to L-479; E-30 to R-478; E-30 to L-477; E-30 to Q-476; E-30 to K-475; E-30 to T-474; E-30 to K-473; E-30 to E-472; E-30 to L-471; E-30 to E-470; E-30 to L-469; E-30 to F-468; E-30 to Q-467; E-30 to N-466; E-30 to Y-465; E-30 to N-464; E-30 to M-463; E-30 to T-462; E-30 to I-461; E-30 to P-460; E-30 to T-459; E-30 to S-458; E-30 to S-457; E-30 to F-456; E-30 to D-455; E-30 to D-454; E-30 to Q-453; E-30 to A-452; E-30 to N-451; E-30 to L-450; E-30 to A-449; E-30 to I-448; E-30 to P-447; E-30 to A-446; E-30 to L-445; E-30 to N-444; E-30 to K-443; E-30 to S-442; E-30 to P-441; E-30 to Y-440; E-30 to Y-439; E-30 to N-438; E-30 to N-437; E-30 to P-436; E-30 to A-435; E-30 to L-434; E-30 to I-433; E-30 to Q-432; E-30 to S-431; E-30 to L-430; E-30 to Q-429; E-30 to N-428; E-30 to E-427; E-30 to K-426; E-30 to A-425; E-30 to K-424; E-30 to I-423; E-30 to T-422; E-30 to A-421; E-30 to L-420; E-30 to T-419; E-30 to Q-418; E-30 to N-417; E-30 to K-416; E-30 to G-415; E-30 to L-414; E-30 to V-413; E-30 to L-412; E-30 to S-411; E-30 to T-410; E-30 to T-409; E-30 to P-408; E-30 to L-407; E-30 to V-406; E-30 to N-405; E-30 to Y-404; E-30 to I-403; E-30 to P-402; E-30 to A-401; E-30 to T-400; E-30 to G-399; E-30 to T-398; E-30 to N-397; E-30 to V-396; E-30 to Y-395; E-30 to R-394; E-30 to I-393; E-30 to N-392; E-30 to A-391; E-30 to N-390; E-30 to L-389; E-30 to R-388; E-30 to A-387; E-30 to T-386; E-30 to D-385; E-30 to A-384; E-30 to T-383; E-30 to N-382; E-30 to L-381; E-30 to G-380; E-30 to M-379; E-30 to T-378; E-30 to E-377; E-30 to A-376; E-30 to W-375; E-30 to T-374; E-30 to R-373; E-30 to E-372; E-30 to G-371; E-30 to A-370; E-30 to L-369; E-30 to S-368; E-30 to L-367; E-30 to S-366; E-30 to H-365; E-30 to D-364; E-30 to I-363; E-30 to

A-362; E-30 to V-361; E-30 to T-360; E-30 to S-359; E-30 to S-358; E-30 to N-357; E-30 to S-356; E-30 to N-355; E-30 to S-354; E-30 to F-353; E-30 to G-352; E-30 to A-351; E-30 to S-350; E-30 to V-349; E-30 to S-348; E-30 to G-347; E-30 to G-346; E-30 to I-345; E-30 to D-344; E-30 to F-343; E-30 to F-342; E-30 to S-341; E-30 to A-340; E-30 to H-339; E-30 to V-338; E-30 to E-337; E-30 to A-336; E-30 to N-335; E-30 to G-334; E-30 to H-333; E-30 to V-332; E-30 to E-331; E-30 to S-330; E-30 to T-329; E-30 to H-328; E-30 to T-327; E-30 to R-326; E-30 to S-325; E-30 to T-324; E-30 to S-323; E-30 to T-322; E-30 to N-321; E-30 to K-320; E-30 to S-319; E-30 to I-318; E-30 to T-317; E-30 to R-316; E-30 to T-315; E-30 to Q-314; E-30 to S-313; E-30 to D-312; E-30 to T-311; E-30 to N-310; E-30 to Q-309; E-30 to T-308; E-30 to S-307; E-30 to Q-306; E-30 to D-305; E-30 to E-304; E-30 to N-303; E-30 to K-302; E-30 to S-301; E-30 to L-300; E-30 to I-299; E-30 to I-298; E-30 to N-297; E-30 to E-296; E-30 to M-295; E-30 to D-294; E-30 to V-293; E-30 to H-292; E-30 to V-291; E-30 to I-290; E-30 to P-289; E-30 to Y-288; E-30 to A-287; E-30 to A-286; E-30 to V-285; E-30 to L-284; E-30 to P-283; E-30 to H-282; E-30 to R-281; E-30 to A-280; E-30 to E-279; E-30 to P-278; E-30 to S-277; E-30 to V-276; E-30 to N-275; E-30 to K-274; E-30 to D-273; E-30 to I-272; E-30 to R-271; E-30 to G-270; E-30 to T-269; E-30 to V-268; E-30 to K-267; E-30 to E-266; E-30 to F-265; E-30 to D-264; E-30 to S-263; E-30 to Y-262; E-30 to P-261; E-30 to D-260; E-30 to S-259; E-30 to A-258; E-30 to T-257; E-30 to S-256; E-30 to W-255; E-30 to K-254; E-30 to E-253; E-30 to P-252; E-30 to S-251; E-30 to S-250; E-30 to K-249; E-30 to Y-248; E-30 to K-247; E-30 to T-246; E-30 to L-245; E-30 to G-244; E-30 to K-243; E-30 to K-242; E-30 to E-241; E-30 to H-240; E-30 to I-239; E-30 to N-238; E-30 to S-237; E-30 to I-236; E-30 to W-235; E-30 to P-234; E-30 to S-233; E-30 to L-232; E-30 to F-231; E-30 to T-230; E-30 to R-229; E-30 to K-228; E-30 to N-227; E-30 to K-226; E-30 to V-225; E-30 to D-224; E-30 to V-223; E-30 to T-222; E-30 to Y-221; E-30 to G-220; E-30 to E-219; E-30 to V-218; E-30 to E-217; E-30 to L-216; E-30 to S-215; E-30 to D-214; E-30 to P-213; E-30 to I-212; E-30 to G-211; E-30 to D-210; E-30 to N-209; E-30 to D-208; E-30 to R-207; E-30 to D-206; E-30 to P-205; E-30 to V-204; E-30 to T-203; E-30 to P-202; E-30 to G-201; E-30 to A-200; E-30 to S-199; E-30 to T-198; E-30 to S-197; E-30 to R-196; E-30 to K-195; E-30 to K-194; E-30 to R-193; E-30 to S-192; E-30 to N-191; E-30 to S-190; E-30 to S-189; E-30 to K-188; E-30 to Q-187; E-30 to K-186; E-30 to L-185; E-30 to E-184; E-30 to P-183; E-30 to L-182; E-30 to Q-181; E-30 to L-180; E-30 to N-179; E-30 to D-178; E-30 to S-177; E-30 to S-176; E-30 to I-175; E-30 to V-174; E-30 to E-173; E-30 to K-172; E-30 to K-171; E-30 to N-170; E-30 to Q-169; E-30 to S-168; E-30 to D-167; E-30 to T-166; E-30 to W-165; E-30 to Y-164; E-30 to L-163; E-30 to K-162; E-30 to F-161; E-30 to D-160; E-30 to L-159; E-30 to G-158; E-30 to K-157; E-30 to E-156; E-30 to T-155; E-30 to P-154; E-30 to N-153; E-30 to E-152; E-30 to R-151; E-30 to Q-150; E-30 to Y-149; E-30 to Q-148; E-30 to I-147; E-30 to K-146; E-30 to I-145; E-30 to Q-144; E-30 to Y-143; E-30 to L-142; E-30 to R-141; E-30 to G-140; E-30 to K-139; E-30 to E-138; E-30 to L-137; E-30 to R-136; E-30 to I-135; E-30 to K-134; E-30 to N-133; E-30 to S-132; E-30 to N-131; E-30 to S-130; E-30 to A-129; E-30 to K-128; E-30 to N-127; E-30 to I-126; E-30 to V-125; E-30 to E-124; E-30 to Q-123; E-30 to D-122; E-30 to D-121; E-30 to V-120; E-30 to W-119; E-30 to M-118; E-30 to T-117; E-30 to V-116; E-30 to H-115; E-30 to N-114; E-30 to D-113; E-30 to A-112; E-30 to S-111; E-30 to T-110; E-30 to A-109; E-30 to F-108; E-30 to T-107; E-30 to Y-106; E-30 to E-105; E-30 to D-104; E-30 to S-103; E-30 to K-102; E-30 to K-101; E-30 to V-100; E-30 to K-99; E-30 to I-98; E-30 to F-97; E-30 to G-96; E-30 to S-95; E-30 to W-94;

E-30 to I-93; E-30 to A-92; E-30 to S-91; E-30 to Q-90; E-30 to F-89; E-30 to Y-88; E-30 to Q-87; E-30 to N-86; E-30 to E-85; E-30 to S-84; E-30 to P-83; E-30 to I-82; E-30 to N-81; E-30 to E-80; E-30 to L-79; E-30 to E-78; E-30 to S-77; E-30 to S-76; E-30 to P-75; E-30 to I-74; E-30 to S-73; E-30 to L-72; E-30 to D-71; E-30 to G-70; E-30 to T-69; E-30 to T-68; E-30 to S-67; E-30 to S-66; E-30 to T-65; E-30 to V-64; E-30 to V-63; E-30 to M-62; E-30 to P-61; E-30 to A-60; E-30 to Q-59; E-30 to F-58; E-30 to N-57; E-30 to L-56; E-30 to D-55; E-30 to S-54; E-30 to F-53; E-30 to Y-52; E-30 to Y-51; E-30 to G-50; E-30 to L-49; E-30 to L-48; E-30 to G-47; E-30 to Q-46; E-30 to S-45; E-30 to S-44; E-30 to S-43; E-30 to E-42; E-30 to S-41; E-30 to E-40; E-30 to N-39; E-30 to L-38; E-30 to L-37; and/or E-30 to R-36 of the amino acid sequence of SEQ ID NO:2.

The invention also provides antibodies that bind polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of a PA polypeptide, which may be described generally as having residues n^1 - m^1 of SEQ ID NO:2, where n^1 and m^1 are integers as described above.

It will be recognized in the art that some amino acid sequence of PA can be varied without significant effect of the structure or function of the protein. If such differences in sequence are contemplated, it should be remembered that there will be critical areas on the protein which determine activity. Such areas will usually comprise residues which make up the ligand binding site or the death domain, or which form tertiary structures which affect these domains.

Thus, the invention further includes antibodies that bind variations of the PA protein which show substantial PA protein activity or which include regions of PA such as the protein fragments discussed below. Such mutants include deletions, insertions, inversions, repeats, and type substitution. Guidance concerning which amino acid changes are likely to be phenotypically silent can be found in Bowie, J. U. et al., *Science* 247:1306-1310 (1990).

Thus, antibodies of the present invention may bind a fragment, derivative, or analog of the polypeptide of SEQ ID NO:2. Such fragments, variants or derivatives may be (i) one in which at least one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue(s), and more preferably at least one but less than ten conserved amino acid residues) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) one in which one or more of the amino acid residues includes a substituent group, or (iii) one in which the mature polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol), or (iv) one in which the additional amino acids are fused to the mature polypeptide, such as an IgG Fc fusion region peptide or leader or secretory sequence or a sequence which is employed for purification of the mature polypeptide or a proprotein sequence. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein.

Of particular interest are substitutions of charged amino acids with another charged amino acid and with neutral or negatively charged amino acids. The latter results in proteins with reduced positive charge to improve the characteristics of the PA protein. The prevention of aggregation is highly desirable. Aggregation of proteins not only results in a loss of activity but can also be problematic when preparing pharmaceutical formulations, because they can be immunogenic. (Pinckard et al., *Clin Exp. Immunol.* 2:331-340 (1967); Robbins et al., *Diabetes* 36:838-845 (1987); Cleland et al. *Crit. Rev. Therapeutic Drug Carrier Systems* 10:307-377 (1993)).

The replacement of amino acids can also change the selectivity of binding to cell surface receptors. Ostade et al., *Nature* 361:266-268 (1993) describes certain mutations resulting in selective binding of TNF-alpha to only one of the two known types of TNF receptors. Thus, the antibodies of the present invention may bind a PA protein that contains one or more amino acid substitutions, deletions or additions, either from natural mutations or human manipulation.

As indicated, changes are preferably of a minor nature, such as conservative amino acid substitutions that do not significantly affect the folding or activity of the protein (see Table 3).

TABLE 3

Conservative Amino Acid Substitutions.	
Aromatic	Phenylalanine
	Tryptophan
	Tyrosine
Hydrophobic	Leucine
	Isoleucine
	Valine
Polar	Glutamine
	Asparagine
Basic	Arginine
	Lysine
	Histidine
Acidic	Aspartic Acid
	Glutamic Acid
Small	Alanine
	Serine
	Threonine
	Methionine
	Glycine

In specific embodiments, the number of substitutions, additions or deletions in the amino acid sequence of SEQ ID NO:2 and/or any of the polypeptides or polypeptide fragments described herein is 75, 70, 60, 50, 40, 35, 30, 25, 20, 15, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 30-20, 20-15, 20-10, 15-10, 10-1, 5-10, 1-5, 1-3 or 1-2.

In specific embodiments, the antibodies of the invention bind PA polypeptides or fragments or variants thereof that contains any one or more of the following conservative mutations in PA: M1 replaced with A, G, I, L, S, T, or V; K2 replaced with H, or R; K3 replaced with H, or R; R4 replaced with H, or K; K5 replaced with H, or R; V6 replaced with A, G, I, L, S, T, or M; L7 replaced with A, G, I, S, T, M, or V; I8 replaced with A, G, L, S, T, M, or V; L10 replaced with A, G, I, S, T, M, or V; M11 replaced with A, G, I, L, S, T, or V; A12 replaced with G, I, L, S, T, M, or V; L13 replaced with A, G, I, S, T, M, or V; S14 replaced with A, G, I, L, T, M, or V; T15 replaced with A, G, I, L, S, M, or V; I16 replaced with A, G, L, S, T, M, or V; L17 replaced with A, G, I, S, T, M, or V; V18 replaced with A, G, I, L, S, T, or M; S19 replaced with A, G, I, L, T, M, or V; S20 replaced with A, G, I, L, T, M, or V; T21 replaced with A, G, I, L, S, M, or V; G22 replaced with A, I, L, S, T, M, or V; N23 replaced with Q; L24 replaced with A, G, I, S, T, M, or V; E25 replaced with D; V26 replaced with A, G, I, L, S, T, or M; I27 replaced with A, G, L, S, T, M, or V; Q28 replaced with N; A29 replaced with G, I, L, S, T, M, or V; E30 replaced with D; V31 replaced with A, G, I, L, S, T, or M; K32 replaced with H, or R; Q33 replaced with N; E34 replaced with D; N35 replaced with Q; R36 replaced with H, or K; L37 replaced with A, G, I, S, T, M, or V; L38 replaced with A, G, I, S, T, M, or V; N39 replaced with Q; E40 replaced with D; S41 replaced with A, G, I, L, T, M, or V; E42 replaced with D; S43 replaced with A, G, I, L, T, M, or V; S44 replaced with A, G, I, L, T, M, or V; S45 replaced with A, G, I, L, T, M,

or V; Q46 replaced with N; G47 replaced with A, I, L, S, T, M, or V; L48 replaced with A, G, I, S, T, M, or V; L49 replaced with A, G, I, S, T, M, or V; G50 replaced with A, I, L, S, T, M, or V; Y51 replaced with F, or W; Y52 replaced with F, or W; F53 replaced with W, or Y; S54 replaced with A, G, I, L, T, M, or V; D55 replaced with E; L56 replaced with A, G, I, S, T, M, or V; N57 replaced with Q; F58 replaced with W, or Y; Q59 replaced with N; A60 replaced with G, I, L, S, T, M, or V; M62 replaced with A, G, I, L, S, T, or V; V63 replaced with A, G, I, L, S, T, or M; V64 replaced with A, G, I, L, S, T, or M; T65 replaced with A, G, I, L, S, M, or V; S66 replaced with A, G, I, L, T, M, or V; S67 replaced with A, G, I, L, T, M, or V; T68 replaced with A, G, I, L, S, M, or V; T69 replaced with A, G, I, L, S, M, or V; G70 replaced with A, I, L, S, T, M, or V; D71 replaced with E; L72 replaced with A, G, I, S, T, M, or V; S73 replaced with A, G, I, L, T, M, or V; I74 replaced with A, G, L, S, T, M, or V; S76 replaced with A, G, I, L, T, M, or V; S77 replaced with A, G, I, L, T, M, or V; E78 replaced with D; L79 replaced with A, G, I, S, T, M, or V; E80 replaced with D; N81 replaced with Q; I82 replaced with A, G, L, S, T, M, or V; S84 replaced with A, G, I, L, T, M, or V; E85 replaced with D; N86 replaced with Q; Q87 replaced with N; Y88 replaced with F, or W; F89 replaced with W, or Y; Q90 replaced with N; S91 replaced with A, G, I, L, T, M, or V; A92 replaced with G, I, L, S, T, M, or V; I93 replaced with A, G, L, S, T, M, or V; W94 replaced with F, or Y; S95 replaced with A, G, I, L, T, M, or V; G96 replaced with A, I, L, S, T, M, or V; F97 replaced with W, or Y; I98 replaced with A, G, L, S, T, M, or V; K99 replaced with H, or R; V110 replaced with A, G, I, L, S, T, or M; K101 replaced with H, or R; K102 replaced with H, or R; S103 replaced with A, G, I, L, T, M, or V; D104 replaced with E; E105 replaced with D; Y106 replaced with F, or W; T107 replaced with A, G, I, L, S, M, or V; F108 replaced with W, or Y; A109 replaced with G, I, L, S, T, M, or V; T110 replaced with A, G, I, L, S, M, or V; S111 replaced with A, G, I, L, T, M, or V; A112 replaced with G, I, L, S, T, M, or V; D113 replaced with E; N114 replaced with Q; H115 replaced with K, or R; V116 replaced with A, G, I, L, S, T, or M; T117 replaced with A, G, I, L, S, M, or V; M118 replaced with A, G, I, L, S, T, or V; W119 replaced with F, or Y; V120 replaced with A, G, I, L, S, T, or M; D121 replaced with E; D122 replaced with E; Q123 replaced with N; E124 replaced with D; V125 replaced with A, G, I, L, S, T, or M; I126 replaced with A, G, L, S, T, M, or V; N127 replaced with Q; K128 replaced with H, or R; A129 replaced with G, I, L, S, T, M, or V; S130 replaced with A, G, I, L, T, M, or V; N131 replaced with Q; S132 replaced with A, G, I, L, T, M, or V; N133 replaced with Q; K134 replaced with H, or R; I135 replaced with A, G, L, S, T, M, or V; R136 replaced with H, or K; L137 replaced with A, G, I, S, T, M, or V; E138 replaced with D; K139 replaced with H, or R; G140 replaced with A, I, L, S, T, M, or V; R141 replaced with H, or K; L142 replaced with A, G, I, S, T, M, or V; Y143 replaced with F, or W; Q144 replaced with N; I145 replaced with A, G, L, S, T, M, or V; K146 replaced with H, or R; I147 replaced with A, G, L, S, T, M, or V; Q148 replaced with N; Y149 replaced with F, or W; Q150 replaced with N; R151 replaced with H, or K; E152 replaced with D; N153 replaced with Q; T155 replaced with A, G, I, L, S, M, or V; E156 replaced with D; K157 replaced with H, or R; G158 replaced with A, I, L, S, T, M, or V; L159 replaced with A, G, I, S, T, M, or V; D160 replaced with E; F161 replaced with W, or Y; K162 replaced with H, or R; L163 replaced with A, G, I, S, T, M, or V; Y164 replaced with F, or W; W165 replaced with F, or Y; T166 replaced with A, G, I, L, S, M, or V; D167 replaced with E; S168 replaced with A, G, I, L, T, M, or V; Q169 replaced with N; N170 replaced with Q; K171 replaced with H, or R; K172 replaced with H, or R;

E173 replaced with D; V174 replaced with A, G, I, L, S, T, or M; I175 replaced with A, G, L, S, T, M, or V; S176 replaced with A, G, I, L, T, M, or V; S177 replaced with A, G, I, L, T, M, or V; D178 replaced with E; N179 replaced with Q; L180#replaced with A, G, I, S, T, M, or V; Q181 replaced with N; L182 replaced with A, G, I, S, T, M, or V; E184 replaced with D; L185 replaced with A, G, I, S, T, M, or V; K186 replaced with H, or R; Q187 replaced with N; K188 replaced with H, or R; S189 replaced with A, G, I, L, T, M, or V; S190 replaced with A, G, I, L, T, M, or V; N191 replaced with Q; S192 replaced with A, G, I, L, T, M, or V; R193 replaced with H, or K; K194 replaced with H, or R; K195 replaced with H, or R; R196 replaced with H, or K; S197 replaced with A, G, I, L, T, M, or V; T198 replaced with A, G, I, L, S, M, or V; S199 replaced with A, G, I, L, T, M, or V; A200 replaced with G, I, L, S, T, M, or V; G201 replaced with A, I, L, S, T, M, or V; T203 replaced with A, G, I, L, S, M, or V; V204 replaced with A, G, I, L, S, T, or M; D206 replaced with E; R207 replaced with H, or K; D208 replaced with E; N209 replaced with Q; D210 replaced with E; G211 replaced with A, I, L, S, T, M, or V; I212 replaced with A, G, L, S, T, M, or V; D214 replaced with E; S215 replaced with A, G, I, L, T, M, or V; L216 replaced with A, G, I, S, T, M, or V; E217 replaced with D; V218 replaced with A, G, I, L, S, T, or M; E219 replaced with D; G220 replaced with A, T, L, S, T, M, or V; Y221 replaced with F, or W; T222 replaced with A, G, I, L, S, M, or V; V223 replaced with A, G, I, L, S, T, or M; D224 replaced with E; V225 replaced with A, G, I, L, S, T, or M; K226 replaced with H, or R; N227 replaced with Q; K228 replaced with H, or R; R229 replaced with H, or K; T230 replaced with A, G, I, L, S, M, or V; F231 replaced with W, or Y; L232 replaced with A, G, I, S, T, M, or V; S233 replaced with A, G, I, L, T, M, or V; W235 replaced with F, or Y; I236 replaced with A, G, L, S, T, M, or V; S237 replaced with A, G, I, L, T, M, or V; N238 replaced with Q; I239 replaced with A, G, L, S, T, M, or V; H240 replaced with K, or R; E241 replaced with D; K242 replaced with H, or R; K243 replaced with H, or R; G244 replaced with A, I, L, S, T, M, or V; L245 replaced with A, G, I, S, T, M, or V; T246 replaced with A, G, I, L, S, M, or V; K247 replaced with H, or R; Y248 replaced with F, or W; K249 replaced with H, or R; S250 replaced with A, G, I, L, T, M, or V; S251 replaced with A, G, I, L, T, M, or V; E253 replaced with D; K254 replaced with H, or R; W255 replaced with F, or Y; S256 replaced with A, G, I, L, T, M, or V; T257 replaced with A, G, I, L, S, M, or V; A258 replaced with G, I, L, S, T, M, or V; S259 replaced with A, G, I, L, T, M, or V; D260 replaced with E; Y262 replaced with F, or W; S263 replaced with A, G, I, L, T, M, or V; D264 replaced with E; F265 replaced with W, or Y; E266 replaced with D; K 267 replaced with H, or R; V268 replaced with A, G, I, L, S, T, or M; T269 replaced with A, G, I, L, S, M, or V; G270 replaced with A, I, L, S, T, M, or V; R271 replaced with H, or K; I272 replaced with A, G, L, S, T, M, or V; D273 replaced with E; K274 replaced with H, or R; N275 replaced with Q; V276 replaced with A, G, I, L, S, T, or M; S277 replaced with A, G, I, L, T, M, or V; E279 replaced with D; A280 replaced with G, I, L, S, T, M, or V; R281 replaced with H, or K; H282 replaced with K, or R; L284 replaced with A, G, I, S, T, M, or V; V285 replaced with A, G, I, L, S, T, or M; A286 replaced with G, I, L, S, T, M, or V; A287 replaced with G, I, L, S, T, M, or V; Y288 replaced with F, or W; I290 replaced with A, G, L, S, T, M, or V; V291 replaced with A, G, I, L, S, T, or M; H292 replaced with K, or R; V293 replaced with A, G, I, L, S, T, or M; D294 replaced with E; M295 replaced with A, G, I, L, S, T, or V; E296 replaced with D; N297 replaced with Q; I298 replaced with A, G, L, S, T, M, or V; I299 replaced with A, G, L, S, T, M, or V; L300 replaced with A, G, I, S, T, M, or V;

S301 replaced with A, G, I, L, T, M, or V; K302 replaced with H, or R; N303 replaced with Q; E304 replaced with D; D305 replaced with E; Q306 replaced with N; S307 replaced with A, G, I, L, T, M, or V; T308 replaced with A, G, I, L, S, M, or V; Q309 replaced with N; N310 replaced with Q; T311 replaced with A, G, I, L, S, M, or V; D312 replaced with E; S313 replaced with A, G, I, L, T, M, or V; Q314 replaced with N; T315 replaced with A, G, I, L, S, M, or V; R316 replaced with H, or K; T317 replaced with A, G, I, L, S, M, or V; 318 replaced with A, G, L, S, T, M, or V; S319 replaced with A, G, I, L, T, M, or V; K320 replaced with H, or R; N321 replaced with Q; T322 replaced with A, G, I, L, S, M, or V; S323 replaced with A, G, T, L, T, M, or V; T324 replaced with A, G, I, L, S, M, or V; S325 replaced with A, G, I, L, T, M, or V; R326 replaced with H, or K; T327 replaced with A, G, I, L, S, M, or V; H328 replaced with K, or R; T329 replaced with A, G, I, L, S, M, or V; S330 replaced with A, G, I, L, T, M, or V; E331 replaced with D; V332 replaced with A, G, I, L, S, T, or M; H333 replaced with K, or R; G334 replaced with A, I, L, S, T, M, or V; N335 replaced with Q; A336 replaced with G, I, L, S, T, M, or V; E337 replaced with D; V338 replaced with A, G, I, L, S, T, or M; H339 replaced with K, or R; A340 replaced with G, I, L, S, T, M, or V; S341 replaced with A, G, I, L, T, M, or V; F342 replaced with W, or Y; F343 replaced with W, or Y; D344 replaced with E; I345 replaced with A, G, L, S, T, M, or V; G346 replaced with A, I, L, S, T, M, or V; G347 replaced with A, I, L, S, T, M, or V; S348 replaced with A, G, I, L, T, M, or V; V349 replaced with A, G, I, L, S, T, or M; S350 replaced with A, G, I, L, T, M, or V; A351 replaced with G, I, L, S, T, M, or V; G352 replaced with A, I, L, S, T, M, or V; F353 replaced with W, or Y; S354 replaced with A, G, I, L, T, M, or V; N355 replaced with Q; S356 replaced with A, G, I, L, T, M, or V; N357 replaced with Q; S358 replaced with A, G, I, L, T, M, or V; S359 replaced with A, G, I, L, T, M, or V; T360 replaced with A, G, I, L, S, M, or V; V361 replaced with A, G, I, L, S, T, or M; A362 replaced with G, I, L, S, T, M, or V; I363 replaced with A, G, L, S, T, M, or V; D364 replaced with E; H365 replaced with K, or R; S366 replaced with A, G, I, L, T, M, or V; L367 replaced with A, G, I, S, T, M, or V; S368 replaced with A, G, I, L, T, M, or V; L369 replaced with A, G, I, S, T, M, or V; A370 replaced with G, I, L, S, T, M, or V; G371 replaced with A, I, L, S, T, M, or V; E372 replaced with D; R373 replaced with H, or K; T374 replaced with A, G, I, L, S, M, or V; W375 replaced with F, or Y; A376 replaced with G, I, L, S, T, M, or V; E377 replaced with D; T378 replaced with A, G, I, L, S, M, or V; M379 replaced with A, G, I, L, S, T, or V; G380 replaced with A, I, L, S, T, M, or V; L381 replaced with A, G, I, S, T, M, or V; N382 replaced with Q; T383 replaced with A, G, I, L, S, M, or V; A384 replaced with G, I, L, S, T, M, or V; D385 replaced with E; T386 replaced with A, G, I, L, S, M, or V; A387 replaced with G, I, L, S, T, M, or V; R388 replaced with H, or K; L389 replaced with A, G, I, S, T, M, or V; N390 replaced with Q; A391 replaced with G, I, L, S, T, M, or V; N392 replaced with Q; I393 replaced with A, G, L, S, T, M, or V; R394 replaced with H, or K; Y395 replaced with F, or W; V396 replaced with A, G, I, L, S, T, or M; N397 replaced with Q; T398 replaced with A, G, I, L, S, M, or V; G399 replaced with A, I, L, S, T, M, or V; T400 replaced with A, G, I, L, S, M, or V; A401 replaced with G, I, L, S, T, M, or V; I403 replaced with A, G, L, S, T, M, or V; Y404 replaced with F, or W; N405 replaced with Q; V406 replaced with A, G, I, L, S, T, or M; L407 replaced with A, G, I, S, T, M, or V; T409 replaced with A, G, I, L, S, M, or V; T410 replaced with A, G, I, L, S, M, or V; S411 replaced with A, G, I, L, T, M, or V; L412 replaced with A, G, I, S, T, M, or V; V413 replaced with A, G, I, L, S, T, or M; L414 replaced with A, G, I, S, T, M, or V; G415 replaced with A, I, L, S, T, M, or V; K416 replaced with H, or

R; N417 replaced with Q; Q418 replaced with N; T419 replaced with A, G, I, L, S, M, or V; L420 replaced with A, G, I, S, T, M, or V; A421 replaced with G, I, L, S, T, M, or V; T422 replaced with A, G, I, L, S, M, or V; I423 replaced with A, G, L, S, T, M, or V; K424 replaced with H, or R; A425 replaced with G, I, L, S, T, M, or V; K426 replaced with H, or R; E427 replaced with D; N428 replaced with Q; Q429 replaced with N; L430 replaced with A, G, I, S, T, M, or V; S431 replaced with A, G, I, L, T, M, or V; Q432 replaced with N; I433 replaced with A, G, L, S, T, M, or V; L434 replaced with A, G, I, S, T, M, or V; A435 replaced with G, I, L, S, T, M, or V; N437 replaced with Q; N438 replaced with Q; Y439 replaced with F, or W; Y440 replaced with F, or W; S442 replaced with A, G, I, L, T, M, or V; K443 replaced with H, or R; N444 replaced with Q; L445 replaced with A, G, I, S, T, M, or V; A446 replaced with G, I, L, S, T, M, or V; I448 replaced with A, G, L, S, T, M, or V; A449 replaced with G, I, L, S, T, M, or V; L450 replaced with A, G, I, S, T, M, or V; N451 replaced with Q; A452 replaced with G, I, L, S, T, M, or V; Q453 replaced with N; D454 replaced with E; D455 replaced with E; F456 replaced with W, or Y; S457 replaced with A, G, I, L, T, M, or V; S458 replaced with A, G, I, L, T, M, or V; T459 replaced with A, G, I, L, S, M, or V; I461 replaced with A, G, L, S, T, M, or V; T462 replaced with A, G, I, L, S, M, or V; M463 replaced with A, G, I, L, S, T, or V; N464 replaced with Q; Y465 replaced with F, or W; N466 replaced with Q; Q467 replaced with N; F468 replaced with W, or Y; L469 replaced with A, G, I, S, T, M, or V; E470 replaced with D; L471 replaced with A, G, I, S, T, M, or V; E472 replaced with D; K473 replaced with H, or R; T474 replaced with A, G, I, L, S, M, or V; K475 replaced with H, or R; Q476 replaced with N; L477 replaced with A, G, I, S, T, M, or V; R478 replaced with H, or K; L479 replaced with A, G, I, S, T, M, or V; D480 replaced with E; T481 replaced with A, G, I, L, S, M, or V; D482 replaced with E; Q483 replaced with N; V484 replaced with A, G, I, L, S, T, or M; Y485 replaced with F, or W; G486 replaced with A, I, L, S, T, M, or V; N487 replaced with Q; I488 replaced with A, G, L, S, T, M, or V; A489 replaced with G, I, L, S, T, M, or V; T490 replaced with A, G, I, L, S, M, or V; Y491 replaced with F, or W; N492 replaced with Q; F493 replaced with W, or Y; E494 replaced with D; N495 replaced with Q; G496 replaced with A, I, L, S, T, M, or V; R497 replaced with H, or K; V498 replaced with A, G, I, L, S, T, or M; R499 replaced with H, or K; V500 replaced with A, G, I, L, S, T, or M; D501 replaced with E; T502 replaced with A, G, I, L, S, M, or V; G503 replaced with A, I, L, S, T, M, or V; S504 replaced with A, G, I, L, T, M, or V; N505 replaced with Q; W506 replaced with F, or Y; S507 replaced with A, G, I, L, T, M, or V; E508 replaced with D; V509 replaced with A, G, I, L, S, T, or M; L510 replaced with A, G, I, S, T, M, or V; Q512 replaced with N; I513 replaced with A, G, L, S, T, M, or V; Q514 replaced with N; E515 replaced with D; T516 replaced with A, G, I, L, S, M, or V; T517 replaced with A, G, I, L, S, M, or V; A518 replaced with G, I, L, S, T, M, or V; R519 replaced with H, or K; I520 replaced with A, G, L, S, T, M, or V; I521 replaced with A, G, L, S, T, M, or V; F522 replaced with W, or Y; N523 replaced with Q; G524 replaced with A, I, L, S, T, M, or V; K525 replaced with H, or R; D526 replaced with E; L527 replaced with A, G, I, S, T, M, or V; N528 replaced with Q; L529 replaced with A, G, I, S, T, M, or V; V530 replaced with A, G, I, L, S, T, or M; E531 replaced with D; R532 replaced with H, or K; R533 replaced with H, or K; I534 replaced with A, G, L, S, T, M, or V; A535 replaced with G, I, L, S, T, M, or V; A536 replaced with G, I, L, S, T, M, or V; V537 replaced with A, G, I, L, S, T, or M; N538 replaced with Q; S540 replaced with A, G, I, L, T, M, or V; D541 replaced with E; L543 replaced with A, G, I, S, T, M, or V;

E544 replaced with D; T545 replaced with A, G, I, L, S, M, or V; T546 replaced with A, G, I, L, S, M, or V; K547 replaced with H, or R; D549 replaced with E; M550 replaced with A, G, I, L, S, T, or V; T551 replaced with A, G, I, L, S, M, or V; L552 replaced with A, G, I, S, T, M, or V; K553 replaced with H, or R; E554 replaced with D; A555 replaced with G, I, L, S, T, M, or V; L556 replaced with A, G, I, S, T, M, or V; K557 replaced with H, or R; I558 replaced with A, G, L, S, T, M, or V; A559 replaced with G, I, L, S, T, M, or V; F560 replaced with W, or Y; G561 replaced with A, I, L, S, T, M, or V; F562 replaced with W, or Y; N563 replaced with Q; E564 replaced with D; N566 replaced with Q; G567 replaced with A, I, L, S, T, M, or V; N568 replaced with Q; L569 replaced with A, G, I, S, T, M, or V; Q570 replaced with N; Y571 replaced with F, or W; Q572 replaced with N; G573 replaced with A, I, L, S, T, M, or V; K574 replaced with H, or R; D575 replaced with E; I576 replaced with A, G, L, S, T, M, or V; T577 replaced with A, G, I, L, S, M, or V; E578 replaced with D; F579 replaced with W, or Y; D580 replaced with E; F581 replaced with W, or Y; N582 replaced with Q; F583 replaced with W, or Y; D584 replaced with E; Q585 replaced with N; Q586 replaced with N; T587 replaced with A, G, I, L, S, M, or V; S588 replaced with A, G, I, L, T, M, or V; Q589 replaced with N; N590 replaced with Q; I591 replaced with A, G, L, S, T, M, or V; K592 replaced with H, or R; N593 replaced with Q; Q594 replaced with N; L595 replaced with A, G, I, S, T, M, or V; A596 replaced with G, I, L, S, T, M, or V; E597 replaced with D; L598 replaced with A, G, I, L, S, T, M, or V; N599 replaced with Q; A600 replaced with G, I, L, S, T, M, or V; T601 replaced with A, G, I, L, S, M, or V; N602 replaced with Q; I603 replaced with A, G, L, S, T, M, or V; Y604 replaced with F, or W; T605 replaced with A, G, I, L, S, M, or V; V606 replaced with A, G, I, L, S, T, or M; L607 replaced with A, G, I, S, T, M, or V; D608 replaced with E; K609 replaced with H, or R; I610 replaced with A, G, L, S, T, M, or V; K611 replaced with H, or R; L612 replaced with A, G, I, S, T, M, or V; N613 replaced with Q; A614 replaced with G, I, L, S, T, M, or V; K615 replaced with H, or R; M616 replaced with A, G, I, L, S, T, or V; N617 replaced with Q; I618 replaced with A, G, L, S, T, M, or V; L619 replaced with A, G, I, S, T, M, or V; I620 replaced with A, G, L, S, T, M, or V; R621 replaced with H, or K; D622 replaced with E; K623 replaced with H, or R; R624 replaced with H, or K; F625 replaced with W, or Y; H626 replaced with K, or R; Y627 replaced with F, or W; D628 replaced with E; R629 replaced with H, or K; N630 replaced with Q; N631 replaced with Q; I632 replaced with A, G, L, S, T, M, or V; A633 replaced with G, I, L, S, T, M, or V; V634 replaced with A, G, I, L, S, T, or M; G635 replaced with A, I, L, S, T, M, or V; A636 replaced with G, I, L, S, T, M, or V; D637 replaced with E; E638 replaced with D; S639 replaced with A, G, I, L, T, M, or V; V640 replaced with A, G, I, L, S, T, or M; V641 replaced with A, G, I, L, S, T, or M; K642 replaced with H, or R; E643 replaced with D; A644 replaced with G, I, L, S, T, M, or V; H645 replaced with K, or R; R646 replaced with H, or K; E647 replaced with D; V648 replaced with A, G, I, L, S, T, or M; I649 replaced with A, G, L, S, T, M, or V; N650 replaced with Q; S651 replaced with A, G, I, L, T, M, or V; S652 replaced with A, G, I, L, T, M, or V; T653 replaced with A, G, I, L, S, M, or V; E654 replaced with D; G655 replaced with A, I, L, S, T, M, or V; L656 replaced with A, G, I, S, T, M, or V; L657 replaced with A, G, I, S, T, M, or V; L658 replaced with A, G, I, S, T, M, or V; N659 replaced with Q; I660 replaced with A, G, L, S, T, M, or V; D661 replaced with E; K662 replaced with H, or R; D663 replaced with E; I664 replaced with A, G, L, S, T, M, or V; R665 replaced with H, or K; K666 replaced with H, or R; I667 replaced with A, G, L, S, T, M, or V; L668 replaced with A, G,

I, S, T, M, or V; S669 replaced with A, G, I, L, T, M, or V; G670 replaced with A, I, L, S, T, M, or V; Y671 replaced with F, or W; 1672 replaced with A, G, L, S, T, M, or V; V673 replaced with A, G, I, L, S, T, or M; E674 replaced with D; 1675 replaced with A, G, L, S, T, M, or V; E676 replaced with D; D677 replaced with E; T678 replaced with A, G, I, L, S, M, or V; E679 replaced with D; G680 replaced with A, I, L, S, T, M, or V; L681 replaced with A, G, I, S, T, M, or V; K682 replaced with H, or R; E683 replaced with D; V684 replaced with A, G, I, L, S, T, or M; 1685 replaced with A, G, L, S, T, M, or V; N686 replaced with Q; D687 replaced with E; R688 replaced with H, or K; Y689 replaced with F, or W; D690 replaced with E; M691 replaced with A, G, I, L, S, T, or V; L692 replaced with A, G, I, S, T, M, or V; N693 replaced with Q; 1694 replaced with A, G, L, S, T, M, or V; S695 replaced with A, G, I, L, T, M, or V; S696 replaced with A, G, I, L, T, M, or V; L697 replaced with A, G, I, S, T, M, or V; R698 replaced with H, or K; Q699 replaced with N; D700 replaced with E; G701 replaced with A, I, L, S, T, M, or V; K702 replaced with H, or R; T703 replaced with A, G, I, L, S, M, or V; F704 replaced with W, or Y; I705 replaced with A, G, L, S, T, M, or V; D706 replaced with E; F707 replaced with W, or Y; K708 replaced with H, or R; K709 replaced with H, or R; Y710 replaced with F, or W; N711 replaced with Q; D712 replaced with E; K713 replaced with H, or R; L714 replaced with A, G, I, S, T, M, or V; L716 replaced with A, G, I, S, T, M, or V; Y717 replaced with F, or W; I718 replaced with A, G, L, S, T, M, or V; S719 replaced with A, G, I, L, T, M, or V; N720 replaced with Q; N722 replaced with Q; Y723 replaced with F, or W; K724 replaced with H, or R; V725 replaced with A, G, I, L, S, T, or M; N726 replaced with Q; V727 replaced with A, G, I, L, S, T, or M; Y728 replaced with F, or W; A729 replaced with G, I, L, S, T, M, or V; V730 replaced with A, G, I, L, S, T, or M; T731 replaced with A, G, I, L, S, M, or V; K732 replaced with H, or R; E733 replaced with D; N734 replaced with Q; T735 replaced with A, G, I, L, S, M, or V; I736 replaced with A, G, L, S, T, M, or V; I737 replaced with A, G, L, S, T, M, or V; N738 replaced with Q; S740 replaced with A, G, I, L, T, M, or V; E741 replaced with D; N742 replaced with Q; G743 replaced with A, I, L, S, T, M, or V; D744 replaced with E; T745 replaced with A, G, I, L, S, M, or V; S746 replaced with A, G, I, L, T, M, or V; T747 replaced with A, G, I, L, S, M, or V; N748 replaced with Q; G749 replaced with A, I, L, S, T, M, or V; I750 replaced with A, G, L, S, T, M, or V; K751 replaced with H, or R; K752 replaced with H, or R; I753 replaced with A, G, L, S, T, M, or V; L754 replaced with A, G, I, S, T, M, or V; I755 replaced with A, G, L, S, T, M, or V; F756 replaced with W, or Y; S757 replaced with A, G, I, L, T, M, or V; K758 replaced with H, or R; K759 replaced with H, or R; G760 replaced with A, I, L, S, T, M, or V; Y761 replaced with F, or W; E762 replaced with D; I763 replaced with A, G, L, S, T, M, or V; G764 replaced with A, I, L, S, T, M, or V; of SEQ ID NO:2.

In specific embodiments, the antibodies of the invention bind PA polypeptides or fragments or variants thereof, that contains any one or more of the following non-conservative mutations in PA: M1 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K2 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K3 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R4 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K5 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V6 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L7 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I8 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P9 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; L10 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; M11 replaced with D, E, H, K, R, N, Q, F, W,

Y, P, or C; A12 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L13 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S14 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T15 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I16 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L17 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V18 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S19 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S20 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T21 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G22 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N23 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L24 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E25 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V26 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I27 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q28 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; A29 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E30 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V31 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K32 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q33 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; E34 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N35 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; R36 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L37 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L38 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N39 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; E40 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S41 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E42 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S43 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S44 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S45 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q46 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G47 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L48 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L49 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G50 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y51 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; Y52 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F53 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S54 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D55 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L56 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N57 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; F58 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; Q59 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; A60 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P61 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; M62 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V63 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V64 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T65 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S66 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S67 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T68 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T69 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G70 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D71 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L72 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S73 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I74 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P75 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; S76 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S77 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F78

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G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L142 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y143 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; Q144 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; I145
replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K146
replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I147 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q148 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W,
Y, P, or C; Y149 replaced with D, E, H, K, R, N, Q, A, G, I, L,
S, T, M, V, P, or C; Q150 replaced with D, E, H, K, R, N, Q, A, G, I,
L, S, T, M, V, F, W, Y, P, or C; R151 replaced with D, E, A, G,
I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E152 replaced with H,
K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N153
replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P,
or C; P154 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V,
N, Q, F, W, Y, or C; T155 replaced with D, E, H, K, R, N, Q,
F, W, Y, P, or C; E156 replaced with H, K, R, A, G, I, L, S, T, M,
V, N, Q, F, W, Y, P, or C; K157 replaced with D, E, A, G,
I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G158 replaced with D,
E, H, K, R, N, Q, F, W, Y, P, or C; L159 replaced with D, E, H,
K, R, N, Q, F, W, Y, P, or C; D160 replaced with H, K, R, A,
G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; F161 replaced with
D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; K162
replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or
C; L163 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;
Y164 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M,
V, P, or C; W165 replaced with D, E, H, K, R, N, Q, A, G, I,
L, S, T, M, V, P, or C; T166 replaced with D, E, H, K, R, N, Q,
F, W, Y, P, or C; D167 replaced with H, K, R, A, G, I, L, S, T,
M, V, N, Q, F, W, Y, P, or C; S168 replaced with D, E, H, K, R,
N, Q, F, W, Y, P, or C; Q169 replaced with D, E, H, K, R, A, G,
I, L, S, T, M, V, F, W, Y, P, or C; N170 replaced with D, E, H,
K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K171 replaced with
D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K172
replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or
C; E173 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F,
W, Y, P, or C; V174 replaced with D, E, H, K, R, N, Q, F, W,
Y, P, or C; I175 replaced with D, E, H, K, R, N, Q, F, W, Y, P,
or C; S176 replaced with D, F, H, K, R, N, Q, F, W, Y, P, or C;
S177 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D178
replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P,
or C; N179 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V,
F, W, Y, P, or C; L180 replaced with D, E, H, K, R, N, Q, F, W,
Y, P, or C; Q181 replaced with D, E, H, K, R, A, G, I, L, S, T,
M, V, F, W, Y, P, or C; L182 replaced with D, E, H, K, R, N, Q,
F, W, Y, P, or C; P183 replaced with D, E, H, K, R, A, G, I, L,
S, T, M, V, N, Q, F, W, Y, or C; E184 replaced with H, K, R, A,
G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L185 replaced with
D, E, H, K, R, N, Q, F, W, Y, P, or C; K186 replaced with D,
E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q187 replaced
with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K188
replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or
C; S189 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;
S190 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N191
replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P,
or C; S192 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;
R193 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y,
P, or C; K194 replaced with D, E, A, G, I, L, S, T, M, V, N, Q,
F, W, Y, P, or C; K195 replaced with D, E, A, G, I, L, S, T, M,
V, N, Q, F, W, Y, P, or C; R196 replaced with D, E, A, G, I, L,
S, T, M, V, N, Q, F, W, Y, P, or C; S197 replaced with D, E, H,
K, R, N, Q, F, W, Y, P, or C; T198 replaced with D, F, H, K, R,
N, Q, F, W, Y, P, or C; S199 replaced with D, E, H, K, R, N, Q,
F, W, Y, P, or C; A200 replaced with D, E, H, K, R, N, Q, F, W,
Y, P, or C; G201 replaced with D, E, H, K, R, N, Q, F, W, Y, P,
or C; P202 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N,
Q, F, W, Y, or C; T203 replaced with D, E, H, K, R, N, Q,

F, W, Y, P, or C; V204 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P205 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; D206 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R207 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D208 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N209 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; D210 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G211 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I212 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P213 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; D214 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S215 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L216 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E217 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V218 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E219 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G220 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y221 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T222 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V223 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D224 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V225 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K226 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N227 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K228 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R229 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T230 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F231 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; L232 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S233 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P234 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; W235 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; I236 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S237 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N238 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; I239 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H240 replaced with D, E, A, G, I, S, T, M, V, N, Q, F, W, Y, P, or C; E241 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K242 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K243 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G244 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L245 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T246 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K247 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Y248 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; K249 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S250 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S251 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P252 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; E253 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K254 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; W255 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S256 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T257 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A258 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S259 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D260 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P261 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; Y262 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S263 replaced with D, F, H, K, R, N, Q, F, W, Y, P, or C; D264 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; F265 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; E266 replaced

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G, I, L, S, T, M, V, N, Q, F, W, Y, or C; I461 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T462 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; M463 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N464 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; Y465 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; N466 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; Q467 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; F468 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; L469 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E470 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L471 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E472 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K473 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T474 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K475 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q476 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L477 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R478 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L479 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D480 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T481 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D482 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q483 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, F, W, Y, P, or C; V484 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y485 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G486 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N487 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; I488 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A489 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T490 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y491 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; N492 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; F493 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; E494 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N495 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G496 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R497 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V498 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R499 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V500 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D501 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T502 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G503 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S504 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N505 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; W506 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S507 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E508 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V509 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L510 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P511 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; Q512 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; I513 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q514 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; E515 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T516 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T517 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A518 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R519 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I520 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I521 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F522 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; N523 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F,

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D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L714 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P715 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; L716 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y717 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; L718 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S719 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N720 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; P721 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; N722 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; Y723 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; K724 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V725 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N726 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; V727 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y728 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; A729 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V730 replaced with D, H, K, R, N, Q, F, W, Y, P, or C; T731 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K732 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E733 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N734 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; T735 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I736 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I737 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N738 replaced with D, E, H, K, R, A, G, I, S, T, M, V, F, W, Y, P, or C; P739 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; S740 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E741 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N742 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G743 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D744 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T745 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S746 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T747 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N748 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G749 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I750 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K751 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K752 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I753 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L754 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I755 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F756 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S757 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K758 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K759 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G760 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y761 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; E762 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I763 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G764 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; of SEQ ID NO:2.

Amino acids in the PA protein that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham and Wells, *Science* 244:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity such as receptor binding or protein multimerization, pore formation, and toxin translocation. Sites that are critical for ligand-receptor binding can also be determined by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith et al., *J. Mol. Biol.* 224:899-904 (1992)) and de

Vos et al. *Science* 255:306-312 (1992)). In preferred embodiments, antibodies of the present invention bind regions of PA that are essential for PA function. In other preferred embodiments, antibodies of the present invention bind regions of PA that are essential for PA function and inhibit or abolish PA function.

Additionally, protein engineering may be employed to improve or alter the characteristics of PA polypeptides. Recombinant DNA technology known to those skilled in the art can be used to create novel mutant proteins or muteins including single or multiple amino acid substitutions, deletions, additions or fusion proteins. Such modified polypeptides can show, e.g., enhanced activity or increased stability. In addition, they may be purified in higher yields and show better solubility than the corresponding natural polypeptide, at least under certain purification and storage conditions. Antibodies of the present invention may bind such modified PA polypeptides.

Non-naturally occurring variants of PA may be produced using art-known mutagenesis techniques, which include, but are not limited to oligonucleotide mediated mutagenesis, alanine scanning, PCR mutagenesis, site directed mutagenesis (see e.g., Carter et al., *Nucl. Acids Res.* 13:4331 (1986); and Zoller et al., *Nuc. Acids Res.* 10:6487 (1982)), cassette mutagenesis (see e.g., Wells et al., *Gene* 34:315 (1985)), restriction selection mutagenesis (see e.g., Wells et al., *Philos. Trans. R. Soc. London SerA* 317:415 (1986)).

Thus, the invention also encompasses antibodies that bind PA derivatives and analogs that have one or more amino acid residues deleted, added, and/or substituted. For example, cysteine residues can be deleted or substituted with another amino acid residue in order to eliminate disulfide bridges; N-linked glycosylation sites can be altered or eliminated to achieve, for example, expression of a homogeneous product that is more easily recovered and purified from yeast hosts which are known to hyperglycosylate N-linked sites. To this end, a variety of amino acid substitutions at one or both of the first or third amino acid positions on any one or more of the glycosylation recognition sequences in the PA polypeptides and/or an amino acid deletion at the second position of any one or more such recognition sequences will prevent glycosylation of the PA at the modified tripeptide sequence (see, e.g., Miyajima et al., *EMBO J.* 5(6):1193-1197). Additionally, one or more of the amino acid residues of PA polypeptides (e.g., arginine and lysine residues) may be deleted or substituted with another residue to eliminate undesired processing by proteases such as, for example, furins or kexins.

The antibodies of the present invention also include antibodies that bind a polypeptide comprising, or alternatively, consisting of a polypeptide comprising, or alternatively, consisting of the polypeptide of SEQ ID NO:2 including the leader; a polypeptide comprising, or alternatively, consisting of the polypeptide of SEQ ID NO:2 minus the amino terminal methionine; a polypeptide comprising, or alternatively, consisting of the polypeptide of SEQ ID NO:2 minus the leader; a polypeptide comprising, or alternatively, consisting of the PA domain I; a polypeptide comprising, or alternatively, consisting of the PA domain II; a polypeptide comprising, or alternatively, consisting of the PA domain III; a polypeptide comprising, or alternatively, consisting of the PA domain IV; a polypeptide comprising, or alternatively, consisting of the PA20 fragment; a polypeptide comprising, or alternatively, consisting of the PA63 fragment; as well as polypeptides which are at least 80% identical, more preferably at least 90% or 95% identical, still more preferably at least 96%, 97%, 98% or 99% identical to the polypeptides described above (the polypeptide and polypeptide fragments of SEQ ID

NO:2), and portions of such polypeptides with at least 30 amino acids and more preferably at least 50 amino acids.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a reference amino acid sequence of a PA polypeptide is intended that the amino acid sequence of the polypeptide is identical to the reference sequence except that the polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the reference amino acid of the PA polypeptide. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a reference amino acid sequence, up to 5% of the amino acid residues in the reference sequence may be deleted or substituted with another amino acid, or a number of amino acids up to 5% of the total amino acid residues in the reference sequence may be inserted into the reference sequence. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence shown in SEQ ID NO:2 can be determined conventionally using known computer programs such as the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, Wis. 53711. When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference amino acid sequence and that gaps in homology of up to 5% of the total number of amino acid residues in the reference sequence are allowed.

In a specific embodiment, the identity between a reference (query) sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, is determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter. According to this embodiment, if the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction is made to the results to take into consideration the fact that the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. A determination of whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of this embodiment. Only residues to the N- and C-termini of the subject

sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence. For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C-termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are made for the purposes of this embodiment.

The present application is also directed to antibodies that bind proteins containing polypeptides at least 90%, 95%, 96%, 97%, 98% or 99% identical to the PA polypeptide sequence set forth herein as n^1-m^1 . In preferred embodiments, the present invention encompasses antibodies that bind proteins containing polypeptides at least 90%, 95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid sequence of the specific PA N- and C-terminal deletions recited herein.

In certain preferred embodiments, antibodies of the invention bind PA fusion proteins as described above wherein the PA portion of the fusion protein are those described as n^1-m^1 herein.

Antibodies of the Invention May Bind Modified PA Polypeptides

It is specifically contemplated that antibodies of the present invention may bind modified forms of PA proteins SEQ ID NO:2). In specific embodiments, antibodies of the present invention bind PA polypeptides (such as those described above) including, but not limited to naturally purified PA polypeptides, PA polypeptides produced by chemical synthetic procedures, and PA polypeptides produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect and mammalian cells using, for example, the recombinant compositions and methods described above. Depending upon the host employed in a recombinant production procedure, the polypeptides may be glycosylated or non-glycosylated. In addition, PA polypeptides may also include an initial modified methionine residue, in some cases as a result of host-mediated processes.

In addition, antibodies of the present invention may bind PA proteins that were chemically synthesized using techniques known in the art (e.g., see Creighton, *Proteins: Structures and Molecular Principles*, W.H. Freeman & Co., N.Y. (1983), and Hunkapiller, et al., *Nature* 310:105-111 (1984)). For example, a peptide corresponding to a fragment of a PA polypeptide can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substi-

tution or addition into the PA polypeptide sequence. Non-classical amino acids include, but are not limited to, the D-isomers of the common amino acids, 2,4-diaminobutyric acid, α -amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, g-Abu, e-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, β -alanine, fluoro-amino acids, designer amino acids such as β -methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

The invention additionally encompasses antibodies that bind PA polypeptides that are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited to, specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, NaBH_4 , acetylation, formylation, oxidation, reduction, metabolic synthesis in the presence of tunicamycin; etc.

Additional post-translational modifications to PA polypeptides for example, e.g., N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends, attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of prokaryotic host cell expression. The polypeptides may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the protein.

Also provided by the invention are antibodies that bind chemically modified derivatives of PA polypeptides which may provide additional advantages such as increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Pat. No. 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kilodalton and about 100 kilodalton (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 50,000, 55,000,

60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kilodalton.

As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Pat. No. 5,643,575; Morpurgo et al., *Appl. Biochem. Biotechnol.* 56:59-72 (1996); Vorobjev et al., *Nucleosides Nucleotides* 18:2745-2750 (1999); and Caliceti et al., *Bioconjug. Chem.* 10:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

The polyethylene glycol molecules (or other chemical moieties) should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a number of attachment methods available to those skilled in the art, e.g., EP 0 401 384, herein incorporated by reference (coupling PEG to G-CSF), see also Malik et al., *Exp. Hematol.* 20:1028-1035 (1992) (reporting pegylation of GM-CSF using tresyl chloride). For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues, glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to a proteins via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) of the protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein.

One may specifically desire proteins chemically modified at the N-terminus. Using polyethylene glycol as an illustration of the present composition, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (or peptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus modification may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

As indicated above, pegylation of the proteins of the invention may be accomplished by any number of means. For example, polyethylene glycol may be attached to the protein either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins are described in Delgado et al., *Crit. Rev. Thera. Drug Carrier Sys.* 9:249-304

(1992); Francis et al., *Intern. J. of Hematol.* 68:1-18 (1998); U.S. Pat. No. 4,002,531; U.S. Pat. No. 5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of which are incorporated herein by reference.

One system for attaching polyethylene glycol directly to amino acid residues of proteins without an intervening linker employs tresylated MPEG, which is produced by the modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride ($\text{ClSO}_2\text{CH}_2\text{CF}_3$). Upon reaction of protein with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the protein. Thus, the invention includes protein-polyethylene glycol conjugates produced by reacting proteins of the invention with a polyethylene glycol molecule having a 2,2,2-trifluoroethane sulphonyl group.

Polyethylene glycol can also be attached to proteins using a number of different intervening linkers. For example, U.S. Pat. No. 5,612,460, the entire disclosure of which is incorporated herein by reference, discloses urethane linkers for connecting polyethylene glycol to proteins. Protein-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the protein by a linker can also be produced by reaction of proteins with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropentylcarbonate, MPEG-p-nitrophenolcarbonate, and various MPEG-succinate derivatives. A number additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins are described in WO 98/32466, the entire disclosure of which is incorporated herein by reference. Pegylated protein products produced using the reaction chemistries set out herein are included within the scope of the invention.

The number of polyethylene glycol moieties attached to each PA polypeptide (i.e., the degree of substitution) may also vary. For example, the pegylated proteins of the invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 17, 20, or more polyethylene glycol molecules. Similarly, the average degree of substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per protein molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado et al., *Crit. Rev. Ther. Drug Carrier Sys.* 9:249-304 (1992).

As mentioned the antibodies of the present invention may bind PA polypeptides that are modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given PA polypeptide. PA polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic PA polypeptides may result from posttranslational natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PRO-

TEINS—STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., *Meth Enzymol* 182:626-646 (1990); Rattan et al., *Ann NY Acad Sci*, 663:48-62 (1992)).

Anti-PA Antibodies

In one embodiment, the invention provides antibodies (e.g., antibodies comprising two heavy chains and two light chains linked together by disulfide bridges) that specifically bind PA (SEQ ID NO:2) or fragments or variants thereof, wherein the amino acid sequence of the heavy chain and the amino acid sequence of the light chain are the same as the amino acid sequence of a heavy chain and a light chain of one or more scFvs or cell lines referred to in Table 1. In another embodiment, the invention provides antibodies (each consisting of two heavy chains and two light chains linked together by disulfide bridges to form an antibody) that specifically bind PA or fragments or variants thereof, wherein the amino acid sequence of the heavy chain or the amino acid sequence of the light chain are the same as the amino acid sequence of a heavy chain or a light chain of one or more scFvs or cell lines referred to in Table 1. Immunospecific binding to PA polypeptides may be determined by immunoassays known in the art or described herein for assaying specific antibody-antigen binding. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies that specifically bind to PA are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies molecules, fragments and/or variants (SEQ ID NOS:57-65).

In one embodiment of the present invention, antibodies that specifically bind to a PA or a fragment or variant thereof, comprise a polypeptide having the amino acid sequence of a heavy chain of at least one of the scFvs referred to in Table 1 or cell lines contained in the ATCC Deposits referred to in Table 1 and/or a light chain of at least one of the scFvs referred to in Table 1 or cell lines contained in the ATCC Deposits referred to in Table 1.

In another embodiment of the present invention, antibodies that specifically bind to PA or a fragment or variant thereof, comprise a polypeptide having the amino acid sequence of any one of the VH domains of at least one of the scFvs referred to in Table 1 or at least one of the recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1 and/or any one of the VL domains of at least one of the scFvs referred to in Table 1 or at least one of the recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1. In preferred embodiments, antibodies of the present invention comprise the amino acid sequence of a VH domain and VL domain from a single scFv referred to in Table 1 or single recombinant antibody expressed by a cell line contained in an ATCC Deposit referred to in Table 1. In alternative embodiments, antibodies of the present invention comprise the amino acid sequence of a VH domain and a VL domain from different scFvs referred to in Table 1 or different recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1. Molecules comprising, or alternatively consisting of, antibody fragments or variants of the VH and/or VL domains of at least one of the scFvs referred to in Table 1 or at least one of the recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1 that specifically bind to PA are also encompassed by the invention, as are nucleic acid molecules

encoding these VH and VL domains, molecules, fragments and/or variants (SEQ ID NOS:57-65).

The present invention also provides antibodies that specifically bind to a polypeptide, or polypeptide fragment or variant of PA, wherein said antibodies comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one, two, three, or more of the VH CDRs contained in a VH domain of one or more scFvs referred to in Table 1 or at least one of the recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1. In particular, the invention provides antibodies that specifically bind PA or fragments or variants thereof comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of a VH CDR1 contained in a VH domain of one or more scFvs or at least one of the recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1. In another embodiment, antibodies that specifically bind PA, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH CDR2 contained in a VH domain of one or more scFvs referred to in Table 1 or one or more recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1. In a preferred embodiment, antibodies that specifically bind PA or fragments or variants thereof, comprise, or alternatively consist of a polypeptide having the amino acid sequence of a VH CDR3 contained in a VH domain of one or more scFvs referred to in Table 1 or one or more recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1. Molecules comprising, or alternatively consisting of, these antibodies, or antibody fragments or variants thereof, that specifically bind to PA or a PA fragment or variant thereof are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments and/or variants (SEQ ID NOS: 57-65).

The present invention also provides antibodies that specifically bind to a PA polypeptide or a polypeptide fragment or variant of PA, wherein said antibodies comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one, two, three, or more of the VL CDRs contained in a VL domain of one or more scFvs referred to in Table 1 or one or more recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1. In particular, the invention provides antibodies that specifically bind PA or a fragment or variant thereof, comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of a VL CDR1 contained in a VL domain of one or more scFvs referred to in Table 1 or one or more recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1. In another embodiment, antibodies that specifically bind PA or a fragment or variant thereof, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VL CDR2 contained in a VL domain of one or more scFvs referred to in Table 1 or one or more recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1. In a preferred embodiment, antibodies that specifically bind PA or a fragment or variant thereof, comprise, or alternatively consist of a polypeptide having the amino acid sequence of a VL CDR3 contained in a VL domain of one or more scFvs referred to in Table 1 or one or more recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1. Molecules comprising, or alternatively consisting of, these antibodies, or antibody fragments or variants thereof, that specifically bind to PA or a PA fragment or variant thereof are also encompassed by the

invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments and/or variants (SEQ ID NOS: 57-65).

The present invention also provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants) that specifically bind to PA polypeptide or a fragment or variant of a PA, wherein said antibodies comprise, or alternatively consist of, one, two, three, or more VH CDRs and one, two, three or more VL CDRs, as contained in a VH domain or VL domain of one or more scFvs referred to in Table 1 or one or more recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1. In particular, the invention provides for antibodies that specifically bind to a PA polypeptide or polypeptide fragment or variant of PA, wherein said antibodies comprise, or alternatively consist of, a VH CDR1 and a VL CDR1, a VH CDR1 and a VL CDR2, a VH CDR1 and a VL CDR3, a VH CDR2 and a VL CDR1, VH CDR2 and VL CDR2, a VH CDR2 and a VL CDR3, a VH CDR3 and a VL CDR1, a VH CDR3 and a VL CDR2, a VH CDR3 and a VL CDR3, or any combination thereof, of the VH CDRs and VL CDRs contained in a VH domain or VL domain of one or more scFvs referred to in Table 1 or one or more recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1. In a preferred embodiment, one or more of these combinations are from the same scFv or the same recombinant antibody expressed by cell line contained in an ATCC deposit as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies, that specifically bind to PA or a fragment or variant thereof are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants (SEQ ID NOS:57-65).

Nucleic Acid Molecules Encoding Anti-PA Antibodies

The present invention also provides for nucleic acid molecules, generally isolated, encoding an antibody of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof).

In a specific embodiment, a nucleic acid molecule of the invention encodes an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), comprising, or alternatively consisting of, a VH domain having an amino acid sequence of any one of the VH domains of at least one of the scFvs referred to in Table 1 or at least one of the recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1 and a VL domain having an amino acid sequence of VL domain of at least one of the scFvs referred to in Table 1 or at least one of the recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1. In another embodiment, a nucleic acid molecule of the invention encodes an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), comprising, or alternatively consisting of, a VH domain having an amino acid sequence of any one of the VH domains of at least one of the scFvs referred to in Table 1 or at least one of the recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1 or a VL domain having an amino acid sequence of a VL domain of at least one of the scFvs referred to in Table 1 or at least one of the recombinant antibodies expressed by the cell lines contained in the ATCC Deposits, referred to in Table 1.

The present invention also provides antibodies that comprise, or alternatively consist of, variants (including derivatives) of the antibody molecules (e.g., the VH domains and/or

VL domains) described herein, which antibodies specifically bind to PA or a fragment or variant thereof. Standard techniques known to those of skill in the art can be used to introduce mutations in the nucleotide sequence encoding a molecule of the invention, including, for example, site-directed mutagenesis and PCR-mediated mutagenesis which result in amino acid substitutions. Preferably, the variants (including derivatives) encode less than 50 amino acid substitutions, less than 40 amino acid substitutions, less than 30 amino acid substitutions, less than 25 amino acid substitutions, less than 20 amino acid substitutions, less than 15 amino acid substitutions, less than 10 amino acid substitutions, less than 5 amino acid substitutions, less than 4 amino acid substitutions, less than 3 amino acid substitutions, or less than 2 amino acid substitutions relative to the reference VH domain, VHCDR1, VHCDR2, VHCDR3, VL domain, VLCDR1, VLCDR2, or VLCDR3. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a side chain with a similar charge. Families of amino acid residues having side chains with similar charges have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for biological activity to identify mutants that retain activity (e.g., the ability to bind PA).

For example, it is possible to introduce mutations only in framework regions or only in CDR regions of an antibody molecule. Introduced mutations may be silent or neutral missense mutations, i.e., have no, or little, effect on an antibody's ability to bind antigen. These types of mutations may be useful to optimize codon usage, or improve a hybridoma's antibody production. Alternatively, non-neutral missense mutations may alter an antibody's ability to bind antigen. The location of most silent and neutral missense mutations is likely to be in the framework regions, while the location of most non-neutral missense mutations is likely to be in CDR, though this is not an absolute requirement. One of skill in the art would be able to design and test mutant molecules with desired properties such as no alteration in antigen binding activity or alteration in binding activity (e.g., improvements in antigen binding activity or change in antibody specificity). Following mutagenesis, the encoded protein may routinely be expressed and the functional and/or biological activity of the encoded protein, (e.g., ability to specifically bind PA) can be determined using techniques described herein or by routinely modifying techniques known in the art.

In a specific embodiment, an antibody of the invention (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), that specifically binds PA or a fragment or variant thereof, comprises, or alternatively consists of, an amino acid sequence encoded by a nucleotide sequence that hybridizes to a nucleotide sequence that is complementary to that encoding one of the VH or VL domains of one or more scFvs referred to in Table 1 or one or more recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1 under stringent conditions, e.g., hybridization to filter-bound DNA in 6x sodium chloride/sodium citrate (SSC) at about

45° C. followed by one or more washes in 0.2xSSC/0.1% SDS at about 50-65° C., under highly stringent conditions, e.g., hybridization to filter-bound nucleic acid in 6xSSC at about 45° C. followed by one or more washes in 0.1xSSC/0.2% SDS at about 68° C., or under other stringent hybridization conditions which are known to those of skill in the art (see, for example, Ausubel, F. M. et al., eds., 1989, *Current Protocols in Molecular Biology*, Vol. 1, Green Publishing Associates, Inc. and John Wiley & Sons, Inc., New York at pages 6.3.1-6.3.6 and 2.10.3). The nucleic acid molecules encoding these antibodies are also encompassed by the invention.

It is well known within the art that polypeptides, or fragments or variants thereof, with similar amino acid sequences often have similar structure and many of the same biological activities. Thus, in one embodiment, an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), that specifically binds to PA or fragments or variants of PA, comprises, or alternatively consists of, a VH domain having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to the amino acid sequence of a VH domain of at least one of the scFvs referred to in Table 1 or at least one of the recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1.

In another embodiment, an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), that specifically binds to PA or a fragment or variant of PA, comprises, or alternatively consists of, a VL domain having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to the amino acid sequence of a VL domain of at least one of the scFvs referred to in Table 1 or at least one of the recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1.

Methods of Producing Antibodies

Antibodies in accordance with the invention were prepared via the utilization of a phage scFv display library. Technologies utilized for achieving the same are disclosed in the patents, applications, and references disclosed herein.

In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In particular, DNA sequences encoding VH and VL domains are amplified from animal cDNA libraries (e.g., human or murine cDNA libraries of lymphoid tissues) or synthetic cDNA libraries. The DNA encoding the VH and VL domains are joined together by an scFv linker by PCR and cloned into a phagemid vector (e.g., pCANTAB 6 or pComb 3 HSS). The vector is electroporated in *E. coli* and the *E. coli* is infected with helper phage. Phage used in these methods are typically filamentous phage including fd and M13 and the VH and VL domains are usually recombinantly fused to either the phage gene III or gene VIII. Phage expressing an antigen binding domain that binds to an antigen of interest (i.e., a PA polypeptide or a fragment thereof) can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Examples of phage display methods that can be used to make the antibodies of the present invention include, but are not limited to, those disclosed in Brinkman et al., *J. Immunol. Methods* 182:41-50 (1995); Ames et al., *J. Immunol. Methods* 184:177-186 (1995); Kettleborough et al., *Eur. J.*

Immunol. 24:952-958 (1994); Persic et al., *Gene* 187 9-18 (1997); Burton et al., *Advances in Immunology* 57:191-280 (1994); PCT application No. PCT/GB91/O1 134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047, WO 92/18719; WO 93/1 1236; WO 95/15982; WO 95/20401; WO97/13844; and U.S. Pat. Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,717; 5,780,225; 5,658,727; 5,735,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

For some uses, such as for in vitro affinity maturation of an antibody of the invention, it may be useful to express the VH and VL domains of one or more scFvs referred to in Table 1 or one or more recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1 as single chain antibodies or Fab fragments in a phage display library. For example, the cDNAs encoding the VH and VL domains of the scFvs referred to in Table 1 or recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1 may be expressed in all possible combinations using a phage display library, allowing for the selection of VH/VL combinations that bind PA polypeptides with preferred binding characteristics such as improved affinity or improved off rates. Additionally, VH and VL segments—and in particular, the CDR regions of the VH and VL domains of the scFvs referred to in Table 1 or recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1, in particular, may be mutated in vitro. Expression of VH and VL domains with “mutant” CDRs in a phage display library allows for the selection of VH/VL combinations that bind PA polypeptides with preferred binding characteristics such as improved affinity or improved off rates.

In particular embodiments, antibodies of the invention comprise the VH and VL domains of the PWD0587 scFv wherein the VH domain contains one or more of the following mutations (using amino acid numbering according to that of SEQ ID NO:53): Q13R, S31W, I100V, and/or E105D. An antibody comprising the PWD0587 VH domain with the Q13R, S31W and I100V mutations and the PWD0587 VL domain, had an approximately 11 fold increase in affinity for the PA antigen compared to an antibody comprising the PWD0587 heavy and light chains. Thus, in specific embodiments, an antibody of the invention comprises the PWD0587 VH domain with the Q13R, S31W and I100V mutations and the PWD0587 VL domain.

An antibody comprising the PWD0587 VH domain with the Q13R and S31W mutations and the PWD0587 VL domain, had an approximately 68 fold increase in affinity for the PA antigen compared to an antibody comprising the PWD0587 heavy and light chains. Thus, in specific embodiments, an antibody of the invention comprises the PWD0587 VH domain with the Q13R and S31W mutations and the PWD0587 VL domain.

An antibody comprising the PWD0587 VH domain with the Q13R, S31W, I100V and E105D mutations and the PWD0587 VL domain, had an approximately 121 fold increase in affinity for the PA antigen compared to an antibody comprising the PWD0587 heavy and light chains. Thus, in specific embodiments, an antibody of the invention comprises the PWD0587 VH domain with the Q13R, S31W, I100V and E105D mutations and the PWD0587 VL domain.

An antibody comprising the PWD0587 VH domain with the Q13R, S31W and E105D mutations and the PWD0587 VL domain, had an approximately 665 fold increase in affinity for the PA antigen compared to an antibody comprising the PWD0587 heavy and light chains. Thus in specific embodi-

ment an antibody of the invention comprises the PWD0587 VH domain with the Q13R, S31W and E105D mutations and the PWD0587 VL domain.

Preliminary testing of the four mutant forms of the PWD0587 antibody with increased affinities for PA compared to the parental PWD0587 (unmutated) antibody, indicated that the mutant PWD0587 antibodies behaved comparably to the parental PWD0587 antibody in, for example, a rubidium release assay (e.g., similar to the assays described in Example 5). In a rat lethal toxin challenge model (similar to the assays described in Example 9) an antibody comprising the PWD0587 VH domain with the Q13R, S31W and E105D mutations and the PWD0587 VL domain was slightly more effective than the parental PWD0587 antibody in preventing lethal toxin induced death.

Additional Methods of Producing Antibodies

Antibodies of the invention (including antibody fragments or variants) can be produced by any method known in the art. For example, it will be appreciated that antibodies in accordance with the present invention can be expressed in cell lines including, but not limited to, myeloma cell lines and hybridoma cell lines. Sequences encoding the cDNAs or genomic clones for the particular antibodies can be used for transformation of a suitable mammalian or nonmammalian host cells or to generate phage display libraries, for example. Additionally, polypeptide antibodies of the invention may be chemically synthesized or produced through the use of recombinant expression systems.

One way to produce the antibodies of the invention would be to clone the VH and/or VL domains of an scFv referred to in Table 1 or recombinant antibody expressed by the cell lines contained in the ATCC Deposits referred to in Table 1. In order to isolate the VH and VL domains from bacteria transfected with a vector containing the scFv, PCR primers complementary to VH or VL nucleotide sequences (See Example 6), may be used to amplify the VH and VL sequences. The PCR products may then be cloned using vectors, for example, which have a PCR product cloning site consisting of a 5' and 3' single T nucleotide overhang, that is complementary to the overhanging single adenine nucleotide added onto the 5' and 3' end of PCR products by many DNA polymerases used for PCR reactions. The VH and VL domains can then be sequenced using conventional methods known in the art. Alternatively, the VH and VL domains may be amplified using vector specific primers designed to amplify the entire scFv, (i.e. the VH domain, linker and VL domain.)

The cloned VH and VL genes may be placed into one or more suitable expression vectors. By way of non-limiting example, PCR primers including VH or VL nucleotide sequences, a restriction site, and a flanking sequence to protect the restriction site may be used to amplify the VH or VL sequences. Utilizing cloning techniques known to those of skill in the art, the PCR amplified VH domains may be cloned into vectors expressing the appropriate immunoglobulin constant region, e.g., the human IgG1 or IgG4 constant region for VH domains, and the human kappa or lambda constant regions for kappa and lambda VL domains, respectively. Preferably, the vectors for expressing the VH or VL domains comprise a promoter suitable to direct expression of the heavy and light chains in the chosen expression system, a secretion signal, a cloning site for the immunoglobulin variable domain, immunoglobulin constant domains, and a selection marker such as neomycin. The VH and VL domains may also be cloned into a single vector expressing the necessary constant regions. The heavy chain conversion vectors and light

chain conversion vectors are then co-transfected into cell lines to generate stable or transient cell lines that express full-length antibodies, e.g., IgG, using techniques known to those of skill in the art (See, for example, Guo et al., *J. Clin. Endocrinol. Metab.* 82:925-31 (1997), and Ames et al., *J. Immunol. Methods* 184:177-86 (1995) which are herein incorporated in their entireties by reference).

The invention provides polynucleotides comprising, or alternatively consisting of, a nucleotide sequence encoding an antibody of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof. The invention also encompasses polynucleotides that hybridize under high stringency, or alternatively, under intermediate or lower stringency hybridization conditions, e.g., as defined supra, to polynucleotides complementary to nucleic acids having a polynucleotide sequence that encodes an antibody of the invention or a fragment or variant thereof.

The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. If the amino acid sequences of the VH domains, VL domains and CDRs thereof, are known, nucleotide sequences encoding these antibodies can be determined using methods well known in the art, i.e., the nucleotide codons known to encode the particular amino acids are assembled in such a way to generate a nucleic acid that encodes the antibody, of the invention. Such a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., *BioTechniques* 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

Alternatively, a polynucleotide encoding an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells or Epstein Barr virus transformed B cell lines that express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

Once the nucleotide sequence of the antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, *Molecular Cloning, A Laboratory Manual*, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. and Ausubel et al., eds., 1998, *Current Protocols in Molecular Biology*, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having a different

amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

In a specific embodiment, VH and VL domains of one or more scFvs referred to in Table 1 or one or more recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1, or fragments or variants thereof, are inserted within framework regions using recombinant DNA techniques known in the art. In a specific embodiment, one, two, three, four, five, six, or more of the CDRs of a VH and/or a VL domain of one or more scFvs referred to in Table 1 or one or more recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1, or fragments or variants thereof, are inserted within framework regions using recombinant DNA techniques known in the art. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., *J. Mol. Biol.* 278: 457-479 (1998) for a listing of human framework regions, the contents of which are hereby incorporated by reference in its entirety). Preferably, the polynucleotides generated by the combination of the framework regions and CDRs encode an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that specifically binds to a PA polypeptide. Preferably, as discussed supra, polynucleotides encoding variants of antibodies or antibody fragments having one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions do not significantly alter binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules, or antibody fragments or variants, lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and fall within the ordinary skill of the art.

The ability to clone and reconstruct megabase-sized human loci in YACs and to introduce them into the mouse germline provides a powerful approach to elucidating the functional components of very large or crudely mapped loci as well as generating useful models of human disease. Furthermore, the utilization of such technology for substitution of mouse loci with their human equivalents could provide unique insights into the expression and regulation of human gene products during development, their communication with other systems, and their involvement in disease induction and progression.

An important practical application of such a strategy is the "humanization" of the mouse humoral immune system. Introduction of human immunoglobulin (Ig) loci into mice in which the endogenous Ig genes have been inactivated offers the opportunity to study the mechanisms underlying programmed expression and assembly of antibodies as well as their role in B cell development. Furthermore, such a strategy could provide an ideal source for production of fully human monoclonal antibodies (mAbs) an important milestone towards fulfilling the promise of antibody therapy in human disease.

Fully human antibodies are expected to minimize the immunogenic and allergic responses intrinsic to mouse or mouse-derivatized Monoclonal antibodies and thus to increase the efficacy and safety of the administered antibodies. The use of fully human antibodies can be expected to provide a substantial advantage in the treatment of chronic and recurring human diseases, such as cancer, which require repeated antibody administrations.

One approach towards this goal was to engineer mouse strains deficient in mouse antibody production with large fragments of the human Ig loci in anticipation that such mice would produce a large repertoire of human antibodies in the absence of mouse antibodies. Large human Ig fragments would preserve the large variable gene diversity as well as the proper regulation of antibody production and expression. By exploiting the mouse machinery for antibody diversification and selection and the lack of immunological tolerance to human proteins, the reproduced human antibody repertoire in these mouse strains should yield high affinity antibodies against any antigen of interest, including human antigens. Using the hybridoma technology, antigen-specific human Monoclonal antibodies with the desired specificity could be readily produced and selected.

This general strategy was demonstrated in connection with the generation of the first XENOMOUSE™ transgenic mouse system strains as published in 1994. See Green et al. *Nature Genetics* 7:13-21 (1994). The XENOMOUSE™ transgenic mouse system strains were engineered with yeast artificial chromosomes (YACS) containing germline configuration fragments of the human heavy chain locus and kappa light chain locus, respectively, which contained core variable and constant region sequences. Id. The human Ig containing YACs proved to be compatible with the mouse system for both rearrangement and expression of antibodies and were capable of substituting for the inactivated mouse Ig genes. This was demonstrated by their ability to induce B-cell development, to produce an adult-like human repertoire of fully human antibodies, and to generate antigen-specific human monoclonal antibodies. These results also suggested that introduction of larger portions of the human Ig loci containing greater numbers of V genes, additional regulatory elements, and human Ig constant regions might recapitulate substantially the full repertoire that is characteristic of the human humoral response to infection and immunization. The work of Green et al. was recently extended to the introduction of greater than approximately 80% of the human antibody repertoire through introduction of megabase sized, germline configuration YAC fragments of the human heavy chain loci and kappa light chain loci, respectively, to produce XENOMOUSE™ transgenic mouse system mice. See Mendez et al. *Nature Genetics* 15:146-156 (1997), Green and Jakobovits *J Exp. Med.* 188:483-495 (1998), Green, *Journal of Immunological Methods* 231:11-23 (1999) and U.S. patent application Ser. No. 08/759,620, filed Dec. 3, 1996, the disclosures of which are hereby incorporated by reference.

Such approach is further discussed and delineated in U.S. patent application Ser. Nos. 07/466,008, filed Jan. 12, 1990, 07/710,515, filed Nov. 8, 1990, 07/919,297, filed Jul. 24, 1992, 07/922,649, filed Jul. 30, 1992, filed 08/031,801, filed Mar. 15, 1993, 08/112,848, filed Aug. 27, 1993, 08/234,145, filed Apr. 28, 1994, 08/376,279, filed Jan. 20, 1995, 08/430,938, Apr. 27, 1995, 08/464,584, filed Jun. 5, 1995, 08/464,582, filed Jun. 5, 1995, 08/471,191, filed Jun. 5, 1995, 08/462,837, filed Jun. 5, 1995, 08/486,853, filed Jun. 5, 1995, 08/486,857, filed Jun. 5, 1995, 08/486,859, filed Jun. 5, 1995, 08/462,513, filed Jun. 5, 1995, 08/724,752, filed Oct. 2, 1996, and 08/759,620, filed Dec. 3, 1996. See also Mendez et al. *Nature Genetics* 15:146-156 (1997) and Green and Jakobovits *J. Exp. Med.* 188:483-495 (1998). See also European Patent No., EP 0463 151 B1, grant published Jun. 12, 1996, International Patent Application No., WO 94/02602, published Feb. 3, 1994, International Patent Application No., WO 96/34096, published Oct. 31, 1996, and WO 98/24893, published Jun.

11, 1998. The disclosures of each of the above-cited patents, applications, and references are hereby incorporated by reference in their entirety.

Human anti-mouse antibody (HAMA) responses have led the industry to prepare chimeric or otherwise humanized antibodies. While chimeric antibodies have a human constant region and a murine variable region, it is expected that certain human anti-chimeric antibody (HACA) responses will be observed, particularly in chronic or multi-dose utilizations of the antibody. Thus, it would be desirable to provide fully human antibodies against PA polypeptides in order to vitiate concerns and/or effects of HAMA or HACA responses.

Monoclonal antibodies specific for PA polypeptides may be prepared using hybridoma technology. (Kohler et al., *Nature* 256:495 (1975); Kohler et al., *Eur. J. Immunol.* 6:511 (1976); Kohler et al., *Eur. J. Immunol.* 6:292 (1976); Hammerling et al., in: *Monoclonal Antibodies and T-Cell Hybridomas*, Elsevier, N.Y., pp. 571-681 (1981)). Briefly, XENOMOUSE™ transgenic mouse system mice may be immunized with PA polypeptides. After immunization, the splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line, such as the myeloma cell line (SP20), available from the ATCC, may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP20), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (*Gastroenterology* 80:225-232 (1981)). The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the PA polypeptides.

For some uses, including in vivo use of antibodies in humans and in vitro detection assays, it may be preferable to use human or chimeric antibodies. Completely human antibodies are particularly desirable for therapeutic treatment of human patients. See also, U.S. Pat. Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50435, WO 98/24893, WO98/16654, WO 96/34096, WO 96/35735, and WO 91/10741; each of which is incorporated herein by reference in its entirety. In a specific embodiment, antibodies of the present invention comprise one or more VH and VL domains of the invention and constant regions from another immunoglobulin molecule, preferably a human immunoglobulin molecule. In a specific embodiment, antibodies of the present invention comprise one or more CDRs corresponding to the VH and VL domains of the invention and framework regions from another immunoglobulin molecule, preferably a human immunoglobulin molecule. In other embodiments, an antibody of the present invention comprises one, two, three, four, five, six or more VL CDRs or VH CDRs corresponding to one or more of the VH or VL domains of one or more scFvs referred to in Table 1 or one or more recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1, or fragments or variants thereof, and framework regions (and, optionally one or more CDRs not present in the scFvs referred to in Table 1 or recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1) from a human immunoglobulin molecule. In a preferred embodiment, an antibody of the present invention comprises a VH CDR3, VL CDR3, or both, corresponding to the same recombinant antibody, or different recombinant antibodies selected from the recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1, or fragments or variants thereof, and framework regions from a human immunoglobulin.

A chimeric antibody is a molecule in which different portions of the antibody are derived from different immunoglobulin molecules such as antibodies having a human variable region and a non-human (e.g., murine) immunoglobulin constant region or vice versa. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, *Science* 229:1202 (1985); Oi et al., *BioTechniques* 4:214 (1986); Gillies et al., *J. Immunol. Methods* 125:191-202 (1989); U.S. Pat. Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entirety. Chimeric antibodies comprising one or more CDRs from human species and framework regions from a non-human immunoglobulin molecule (e.g., framework regions from a murine, canine or feline immunoglobulin molecule) (or vice versa) can be produced using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Pat. Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, *Molecular Immunology* 28(4/5):489-498 (1991); Studnicka et al., *Protein Engineering* 7(6):805-814 (1994); Roguska et al., *PNAS* 91:969-973 (1994)), and chain shuffling (U.S. Pat. No. 5,565,352). In a preferred embodiment, chimeric antibodies comprise a human CDR3 having an amino acid sequence of any one of the VH CDR3s or VL CDR3s of a VH or VL domain of one or more of the scFvs referred to in Table 1, or a variant thereof, and non-human framework regions or human framework regions different from those of the frameworks in the corresponding scFv disclosed in Table 1. Often, framework residues in the framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Pat. No. 5,585,089; Riechmann et al., *Nature* 352:323 (1988), which are incorporated herein by reference in their entirety.)

Intrabodies are antibodies, often scFvs, that are expressed from a recombinant nucleic acid molecule and engineered to be retained intracellularly (e.g., retained in the cytoplasm, endoplasmic reticulum, or periplasm). Intrabodies may be used, for example, to ablate the function of a protein to which the intrabody binds. The expression of intrabodies may also be regulated through the use of inducible promoters in the nucleic acid expression vector comprising the intrabody. Intrabodies of the invention can be produced using methods known in the art, such as those disclosed and reviewed in Chen et al., *Hum. Gene Ther.* 5:595-601 (1994); Marasco, W. A., *Gene Ther.* 4:11-15 (1997); Rondon and Marasco, *Annu. Rev. Microbiol.* 51:257-283 (1997); Proba et al., *J. Mol. Biol.* 275:245-253 (1998); Cohen et al., *Oncogene* 17:2445-2456 (1998); Ohage and Steipe, *J. Mol. Biol.* 291:1119-1128 (1999); Ohage et al., *J. Mol. Biol.* 291:1129-1134 (1999); Wirtz and Steipe, *Protein Sci.* 8:2245-2250 (1999); Zhu et al., *J. Immunol. Methods* 231:207-222 (1999); and references cited therein.

Recombinant expression of an antibody of the invention (including antibody fragments or variants thereof (e.g., a heavy or light chain of an antibody of the invention), requires construction of an expression vector(s) containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule (e.g., a whole antibody, a heavy or light chain of an antibody, or portion thereof (preferably, but not necessarily, containing the heavy or light chain variable domain)), of the invention has been obtained, the

vector(s) for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention (e.g., a whole antibody, a heavy or light chain of an antibody, a heavy or light chain variable domain of an antibody, or a portion thereof, or a heavy or light chain CDR, a single chain Fv, or fragments or variants thereof), operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Pat. No. 5,122,464, the contents of each of which are hereby incorporated by reference in its entirety) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy chain, the entire light chain, or both the entire heavy and light chains.

The expression vector(s) is(are) transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing polynucleotide(s) encoding an antibody of the invention (e.g., whole antibody, a heavy or light chain thereof, or portion thereof, or a single chain antibody, or a fragment or variant thereof), operably linked to a heterologous promoter. In preferred embodiments, for the expression of entire antibody molecules, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention in situ. These include, but are not limited to, bacteriophage particles engineered to express antibody fragments or variants thereof (single chain antibodies), microorganisms such as bacteria (e.g., *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3, NS0 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as *Escherichia coli*, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are

used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foelcking et al., *Gene* 45:101 (1986); Cockett et al., *Bio/Technology* 8:2 (1990); Bebbington et al., *Bio/Techniques* 10:169 (1992); Keen and Hale, *Cytotechnology* 18:207 (1996)). These references are incorporated in their entireties by reference herein.

In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited to, the *E. coli* expression vector pUR278 (Ruther et al., *EMBO J.* 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, *Nucleic Acids Res.* 13:3101-3109 (1985); Van Heeke & Schuster, *J. Biol. Chem.* 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

In an insect system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) may be used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. Antibody coding sequences may be cloned individually into non-essential regions (for example, the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example, the polyhedrin promoter).

In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by in vitro or in vivo recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts (e.g., see Logan & Shenk, *Proc. Natl. Acad. Sci. USA* 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see, e.g., Bittner et al., *Methods in Enzymol.* 153:51-544 (1987)).

In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g.,

cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include, but are not limited to, CHO, VERY, BHK, HeLa, COS, NSO, MDCK, 293, 3T3, W138, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and Hs578Bst.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compositions that interact directly or indirectly with the antibody molecule.

A number of selection systems may be used, including but not limited to, the herpes simplex virus thymidine kinase (Wigler et al., *Cell* 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, *Proc. Natl. Acad. Sci. USA* 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., *Cell* 22:8 17 (1980)) genes can be employed in tk-, hgpRT- or apRT- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., *Natl. Acad. Sci. USA* 77:357 (1980); O'Hare et al., *Proc. Natl. Acad. Sci. USA* 78:1527 (1981)); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, *Proc. Natl. Acad. Sci. USA* 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 (*Clinical Pharmacy* 12:488-505; Wu and Wu, *Biotherapy* 3:87-95 (1991); Tolstoshev, *Ann. Rev. Pharmacol. Toxicol.* 32:573-596 (1993); Mulligan, *Science* 260: 926-932 (1993); and Morgan and Anderson, *Ann. Rev. Biochem.* 62: 191-217 (1993); TIB TECH 11(5):155-2 15 (May, 1993)); and hygR, which confers resistance to hygromycin (Santerre et al., *Gene* 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.), *Current Protocols in Molecular Biology*, John Wiley & Sons, NY (1993); Kriegler, *Gene Transfer and Expression, A Laboratory Manual*, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), *Current Protocols in Human Genetics*, John Wiley & Sons, NY (1994); Colberre-Garapin et al., *J. Mol. Biol.* 150:1 (1981), which are incorporated by reference herein in their entireties.

The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington

ton and Hentschel, "The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells" in *DNA Cloning*, Vol. 3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the coding sequence of the antibody, production of the antibody will also increase (Crouse et al., *Mol. Cell. Biol.* 3:257 (1983)).

Vectors which use glutamine synthase (GS) or DHFR as the selectable markers can be amplified in the presence of the drugs methionine sulfoximine or methotrexate, respectively. An advantage of glutamine synthase based vectors are the availability of cell lines (e.g., the murine myeloma cell line, NS0) which are glutamine synthase negative. Glutamine synthase expression systems can also function in glutamine synthase expressing cells (e.g. Chinese Hamster Ovary (CHO) cells) by providing additional inhibitor to prevent the functioning of the endogenous gene. A glutamine synthase expression system and components thereof are detailed in PCT publications: WO87/04462; WO86/05807; WO89/01036; WO89/10404; and WO91/06657 which are incorporated in their entireties by reference herein. Additionally, glutamine synthase expression vectors that may be used according to the present invention are commercially available from suppliers, including, for example Lonza Biologics, Inc. (Portsmouth, N.H.). Expression and production of monoclonal antibodies using a GS expression system in murine myeloma cells is described in Bebbington et al., *Bio/technology* 10:169 (1992) and in Biblia and Robinson *Biotechnol. Prog.* 11:1 (1995) which are incorporated in their entireties by reference herein.

The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain is preferably placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, *Nature* 322:52 (1986); Kohler, *Proc. Natl. Acad. Sci. USA* 77:2 197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

Once an antibody molecule of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) has been chemically synthesized or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, or more generally, a protein molecule, such as, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. Further, the antibodies of the present invention may be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

Antibodies of the present invention include naturally purified products, products of chemical synthetic procedures, and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect and mammalian cells. Depending upon the host employed in a recombinant production procedure, the antibodies of the present invention may be

glycosylated or may be non-glycosylated. In addition, antibodies of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes.

Antibodies of the invention can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, *Proteins: Structures and Molecular Principles*, W.H. Freeman & Co., N.Y., and Hunkapiller, M., et al., 1984, *Nature* 310: 105-111). For example, a peptide corresponding to a fragment of an antibody of the invention can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the antibody polypeptide sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4-diaminobutyric acid, α -amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, g-Abu, e-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, β -alanine, fluoro-amino acids, designer amino acids such as β -methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

The invention encompasses antibodies which are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, NaBH₄, acetylation, formylation, oxidation, reduction, metabolic synthesis in the presence of tunicamycin, etc.

Additional post-translational modifications encompassed by the invention include, for example, e.g., N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of prokaryotic host cell expression. The antibodies may also be modified with a detectable label, such as an enzymatic, fluorescent, radioisotopic or affinity label to allow for detection and isolation of the antibody.

Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, glucose oxidase or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include biotin, umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include a radioactive metal ion, e.g., α -emitters such as, for example, ²¹³Bi, or other radioisotopes such as, for example, iodine (¹³¹I, ¹²⁵I, ¹²³I, ¹²¹I), carbon (¹⁴C), sulfur (³⁵S), tritium (³H), indium (¹¹⁵mIn, ¹¹³mIn, ¹¹²In, ¹¹¹In), and technetium (⁹⁹Tc, ^{99m}Tc), thallium (²⁰¹Tl), gallium (⁶⁸Ga, ⁶⁷Ga), palladium (¹⁰³Pd), molybdenum (⁹⁹Mo), xenon (¹³³Xe), fluorine (¹⁸F), ¹⁵³Sm, ¹⁷⁷Lu, ¹⁵⁹Gd, ¹⁴⁹Pm, ¹⁴⁰La, ¹⁷⁵Yb,

166Ho, 90Y, 47Sc, 186Re, 188Re, 142Pr, 105Rh, 97Ru, 68Ge, 57Co, 65Zn, 85Sr, 32P, 153Gd, 169Yb, 51Cr, 54Mn, 75Se, 113Sn, and 117Tm.

In specific embodiments, antibodies of the invention may be labeled with Europium. For example, antibodies of the invention may be labelled with Europium using the DELFIA Eu-labeling kit (catalog #1244-302, Perkin Elmer Life Sciences, Boston, Mass.) following manufacturer's instructions.

In specific embodiments, antibodies of the invention are attached to macrocyclic chelators useful for conjugating radiometal ions, including but not limited to, 111In, 177Lu, 90Y, 166Ho, 153Sm, 215Bi and 225Ac to polypeptides. In a preferred embodiment, the radiometal ion associated with the macrocyclic chelators attached to antibodies of the invention is 111In. In another preferred embodiment, the radiometal ion associated with the macrocyclic chelator attached to antibodies polypeptides of the invention is 90Y. In specific embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA). In specific embodiments, the macrocyclic chelator is \square -(5-isothiocyanato-2-methoxyphenyl)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid. In other specific embodiments, the DOTA is attached to the antibody of the invention via a linker molecule. Examples of linker molecules useful for conjugating a macrocyclic chelator such as DOTA to a polypeptide are commonly known in the art—see, for example, DeNardo et al., *Clin Cancer Res.* 4(10):2483-90, 1998; Peterson et al., *Bioconjug. Chem.* 10(4):553-7, 1999; and Zimmerman et al., *Nucl. Med. Biol.* 26(8):943-50, 1999 which are hereby incorporated by reference in their entirety. In addition, U.S. Pat. Nos. 5,652,361 and 5,756,065, which disclose chelating agents that may be conjugated to antibodies, and methods for making and using them, are hereby incorporated by reference in their entireties.

In one embodiment, antibodies of the invention are labeled with biotin. In other related embodiments, biotinylated antibodies of the invention may be used, for example, as an imaging agent or as a means of identifying one or more TRAIL receptor coreceptor or ligand molecules.

Also provided by the invention are chemically modified derivatives of antibodies of the invention which may provide additional advantages such as increased solubility, stability and in vivo or in vitro circulating time of the polypeptide, or decreased immunogenicity (see U.S. Pat. No. 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The antibodies may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2560, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500,

11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa.

As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Pat. No. 5,643,575; Morpurgo et al., *Appl. Biochem. Biotechnol.* 56:59-72 (1996); Vorobjev et al., *Nucleosides Nucleotides* 18:2745-2750 (1999); and Caliceti et al., *Bioconjug. Chem.* 10:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

The polyethylene glycol molecules (or other chemical moieties) should be attached to the antibody with consideration of effects on functional or antigenic domains of the antibody. There are a number of attachment methods available to those skilled in the art, e.g., EP 0 401 384, herein incorporated by reference (coupling PEG to G-CSF), see also Malik et al., *Exp. Hematol.* 20:1028-1035 (1992) (reporting pegylation of GM-CSF using tresyl chloride). For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include, for example, lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues, glutamic acid residues, and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

As suggested above, polyethylene glycol may be attached to proteins, e.g., antibodies, via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to a proteins via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) of the protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein.

One may specifically desire antibodies chemically modified at the N-terminus of either the heavy chain or the light chain or both. Using polyethylene glycol as an illustration, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (or peptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective chemical modification at the N-terminus may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

As indicated above, pegylation of the antibodies of the invention may be accomplished by any number of means. For

example, polyethylene glycol may be attached to the antibody either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins are described in Delgado et al., Crit. Rev. Thera. Drug Carrier Sys. 9:249-304 (1992); Francis et al., Intern. J. of Hematol. 68:1-18 (1998); U.S. Pat. No. 4,002,531; U.S. Pat. No. 5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of which are incorporated herein by reference.

One system for attaching polyethylene glycol directly to amino acid residues of antibodies without an intervening linker employs tresylated MPEG, which is produced by the modification of monomethoxy polyethylene glycol (MPEG) using tresylchloride (ClSO₂CH₂CF₃). Upon reaction of protein with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the protein. Thus, the invention includes antibody-polyethylene glycol conjugates produced by reacting antibodies of the invention with a polyethylene glycol molecule having a 2,2,2-trifluoroethane sulphonyl group.

Polyethylene glycol can also be attached to antibodies using a number of different intervening linkers. For example, U.S. Pat. No. 5,612,460, the entire disclosure of which is incorporated herein by reference, discloses urethane linkers for connecting polyethylene glycol to proteins. Antibody-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the antibody by a linker can also be produced by reaction of antibodies with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG-p-nitrophenolcarbonate, and various MPEG-succinate derivatives. A number additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins are described in WO 98/32466, the entire disclosure of which is incorporated herein by reference. Pegylated antibody products produced using the reaction chemistries set out herein are included within the scope of the invention.

The number of polyethylene glycol moieties attached to each antibody of the invention (i.e., the degree of substitution) may also vary. For example, the pegylated antibodies of the invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 17, 20, or more polyethylene glycol molecules. Similarly, the average degree of substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per antibody molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado et al., Crit. Rev. Thera. Drug Carrier Sys. 9:249-304 (1992).

Characterization of Anti-PA Antibodies

Antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may also be described or specified in terms of their binding to PA polypeptides or fragments or variants of PA polypeptides. In specific embodiments, antibodies of the invention bind PA polypeptides, or fragments or variants thereof, with a dissociation constant or K_D of less than or equal to 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, or 10^{-5} M. More preferably, antibodies of the invention bind PA polypeptides or fragments or variants thereof with a dissociation constant or K_D less than or equal to 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, or 10^{-8} M. Even more preferably, antibodies of the invention bind PA polypeptides or fragments or variants thereof with a dissociation constant or K_D less than or equal to 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12}

M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, or 10^{-15} M. The invention encompasses antibodies that bind PA polypeptides with a dissociation constant or K_D that is within any one of the ranges that are between each of the individual recited values.

In specific embodiments, antibodies of the invention bind PA polypeptides or fragments or variants thereof with an off rate (k_{off}) of less than or equal to 5×10^{-2} sec⁻¹, 10^{-2} sec⁻¹, 5×10^{-3} sec⁻¹ or 10^{-3} sec⁻¹. More preferably, antibodies of the invention bind PA polypeptides or fragments or variants thereof with an off rate (k_{off}) less than or equal to 5×10^{-4} sec⁻¹, 10^{-4} sec⁻¹, 5×10^{-5} sec⁻¹, or 10^{-5} sec⁻¹, 5×10^{-6} sec⁻¹, 10^{-6} sec⁻¹, 5×10^{-7} sec⁻¹ or 10^{-7} sec⁻¹. The invention encompasses antibodies that bind PA polypeptides with an off rate (k_{off}) that is within any one of the ranges that are between each of the individual recited values.

In other embodiments, antibodies of the invention bind PA polypeptides or fragments or variants thereof with an on rate (k_{on}) of greater than or equal to 10^3 M⁻¹sec⁻¹, 5×10^3 M⁻¹sec⁻¹, 10^4 M⁻¹sec⁻¹ or 5×10^4 M⁻¹sec⁻¹. More preferably, antibodies of the invention bind PA polypeptides or fragments or variants thereof with an on rate (k_{on}) greater than or equal to 10^5 M⁻¹sec⁻¹, 5×10^5 M⁻¹sec⁻¹, 10^6 M⁻¹sec⁻¹, or 5×10^6 M⁻¹sec⁻¹ or 10^7 M⁻¹sec⁻¹. The invention encompasses antibodies that bind PA polypeptides with on rate (k_{on}) that is within any one of the ranges that are between each of the individual recited values.

In preferred embodiments, the antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), specifically bind to PA polypeptides and do not cross-react with any other antigens. In preferred embodiments, the antibodies of the invention specifically bind to PA polypeptides (e.g., SEQ ID NO:2 or fragments or variants thereof) and do not cross-react with other bacterial binary toxins (A-B toxins) such as those from *Clostridium difficile*, *Clostridium perfringens*, *Clostridium spiroforme*, *Clostridium botulinum*, *Bacillus cereus* and/or *Bacillus thuringiensis*.

In another embodiment, the antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), specifically bind to PA polypeptides and cross-react with other antigens. In other embodiments, the antibodies of the invention specifically bind to PA polypeptides (e.g., SEQ ID NO:2 or fragments or variants thereof) and cross-react with other bacterial binary toxins (A-B toxins) such as those from *Clostridium difficile*, *Clostridium perfringens*, *Clostridium spiroforme*, *Clostridium botulinum*, *Bacillus cereus* and/or *Bacillus thuringiensis*.

In a preferred embodiment, antibodies of the invention preferentially bind PA (SEQ ID NO:2), or fragments and variants thereof relative to their ability to bind other antigens (e.g., other bacterial binary toxins (A-B toxins) such as those from *Clostridium difficile*, *Clostridium perfringens*, *Clostridium spiroforme*, *Clostridium botulinum*, *Bacillus cereus* and/or *Bacillus thuringiensis*). An antibody's ability to preferentially bind one antigen compared to another antigen may be determined using any method known in the art.

By way of non-limiting example, an antibody may be considered to bind a first antigen preferentially if it binds said first antigen with a dissociation constant (K_D) that is less than the antibody's K_D for the second antigen. In another non-limiting embodiment, an antibody may be considered to bind a first antigen preferentially if it binds said first antigen with an affinity (i.e., K_D) that is at least one order of magnitude less than the antibody's K_D for the second antigen. In another non-limiting embodiment, an antibody may be considered to

bind a first antigen preferentially if it binds said first antigen with an affinity (i.e., K_D) that is at least two orders of magnitude less than the antibody's K_D for the second antigen.

In another non-limiting embodiment, an antibody may be considered to bind a first antigen preferentially if it binds said first antigen with an off rate (k_{off}) that is less than the antibody's k_{off} for the second antigen. In another non-limiting embodiment, an antibody may be considered to bind a first antigen preferentially if it binds said first antigen with a k_{off} that is at least one order of magnitude less than the antibody's k_{off} for the second antigen. In another non-limiting embodiment, an antibody may be considered to bind a first antigen preferentially if it binds said first antigen with a k_{off} that is at least two orders of magnitude less than the antibody's k_{off} for the second antigen.

The invention also encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that have one or more of the same biological characteristics as one or more of the antibodies described herein. By "biological characteristics" is meant, the *in vitro* or *in vivo* activities or properties of the antibodies, such as, for example, the ability to bind to PA polypeptides (e.g., either the PA83 or PA63 form of PA); or the ability to inhibit the cleavage of the PA83 into PA20 and PA63 by proteases such as trypsin or furin. Additionally, antibodies of the invention may: prevent oligomerization of PA63, especially heptamerization of PA63; inhibit or abolish the ability of PA63 to bind to an anthrax receptor, e.g., ATR and/or CMG2 (See Example 3); inhibit or abolish the ability of PA63 to bind LF or EF; inhibit or abolish the ability of PA63 to form pores in membranes (see Example 5); inhibit or abolish the ability of lethal toxin (LT) to kill cells, such as macrophages (see Example 8), or animals (see Examples 9-12); or inhibit or abolish the ability of PA heptamers to translocate LF or EF across a membrane (see Example 13). Optionally, the antibodies of the invention will bind to the same epitope as at least one of the antibodies specifically referred to herein. Such epitope binding can be routinely determined using assays known in the art.

The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that inhibit or abolish biological activities of PA. By "biological activities of PA" is meant, for example, the ability of PA83 to be cleaved by proteases into PA20 and PA63 fragments; the ability of PA to bind to ATR and/or CMG2; the ability of PA or PA63 to oligomerize, especially to heptamerize; the ability of PA63 to bind LF or EF; the ability of PA63 heptamers to form pores in a membrane; and/or the ability of PA heptamers to translocate EF or LF across a membrane. In one embodiment, an antibody that inhibits or abolishes biological activities of PA comprises, or alternatively consists of a VH and/or a VL domain of at least one of the scFvs referred to in Table 1 or recombinant antibodies expressed by the cell lines referred to in Table 1, or a fragment or variant thereof. In a specific embodiment, an antibody that inhibits or abolishes biological activities of PA comprises, or alternatively consists of a VH and a VL domain of any one of the scFvs referred to in Table 1 or recombinant antibodies expressed by the cell lines referred to in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that inhibit the cleavage of the PA83 into PA20 and PA63 by proteases such as trypsin or furin. See, e.g., Example 2 wherein an antibody that binds

peptides that span the RKKR (residues 193-196 of SEQ ID NO:2) cleavage site of PA may be predictive of an antibody's ability to inhibit the cleavage of PA by proteases. Alternatively, a PA cleavage assay is described in *J. Biol. Chem.* (1992), 267:16396-402, which is hereby incorporated by reference in its entirety. In one embodiment, an antibody that inhibits the cleavage of the PA83 into PA20 and PA63 comprises, or alternatively consists of a VH and/or a VL domain of at least one of the scFvs referred to in Table 1 or recombinant antibodies expressed by the cell lines referred to in Table 1, or a fragment or variant thereof. In a specific embodiment, an antibody that inhibits the cleavage of the PA83 into PA20 and PA63 comprises, or alternatively consists of a VH and a VL domain of any one of the scFvs referred to in Table 1 or recombinant antibodies expressed by the cell lines referred to in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that block or inhibit the binding of PA to ATR and/or CMG2 (e.g., see Example 3). In one embodiment, an antibody that blocks or inhibits the binding of PA to ATR and/or CMG2 comprises, or alternatively consists of a VH and/or a VL domain of at least one of the scFvs referred to in Table 1 or at least one of the recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1, or a fragment or variant thereof. In a specific embodiment, an antibody that blocks or inhibits the binding of PA to ATR and/or CMG2 comprises, or alternatively consists of a VH and a VL domain of any one of the scFvs referred to in Table 1 or any one of the recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that block or inhibit the ability of PA or PA63 to heptamerize. In one embodiment, an antibody that blocks or inhibits the ability of PA or PA63 to heptamerize comprises, or alternatively consists of a VH and/or a VL domain of at least one of the scFvs referred to in Table 1 or at least one of the recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1, or a fragment or variant thereof. In a specific embodiment, an antibody that blocks or inhibits the ability of PA63 to heptamerize comprises, or alternatively consists of a VH and a VL domain of any one of the scFvs referred to in Table 1 or any one of the recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that block or inhibit the ability of PA63 to bind EF or LF. In one embodiment, an antibody that blocks or inhibits the ability of PA63 to bind EF or LF comprises, or alternatively consists of a VH and/or a VL domain of at least one of the scFvs referred to in Table 1 or at least one of the recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1, or a fragment or variant thereof. In a specific embodiment, an antibody that blocks or inhibits the ability of PA63 to bind EF or LF comprises, or alternatively consists of a VH and a VL domain of any one of the scFvs referred to in Table 1 or any one of the recombinant antibodies expressed by the cell lines

contained in the ATCC Deposits referred to in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that block or inhibit the ability of PA63 heptamers to form pores in membranes. In one embodiment, an antibody that blocks or inhibits the ability of PA63 heptamers to form pores in membranes comprises, or alternatively consists of a VH and/or a VL domain of at least one of the scFvs referred to in Table 1 or at least one of the recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1, or a fragment or variant thereof. In a specific embodiment, an antibody that blocks or inhibits the ability of PA63 heptamers to form pores in membranes comprises, or alternatively consists of a VH and a VL domain of any one of the scFvs referred to in Table 1 or any one of the recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that block or inhibit the ability of PA63 heptamers to translocate EF or LF across membranes. In one embodiment, an antibody that blocks or inhibits the ability of PA63 heptamers to translocate EF or LF across membranes comprises, or alternatively consists of a VH and/or a VL domain of at least one of the scFvs referred to in Table 1 or at least one of the recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1, or a fragment or variant thereof. In a specific embodiment, an antibody that blocks or inhibits the ability of PA63 heptamers to translocate EF or LF across membranes comprises, or alternatively consists of a VH and a VL domain of any one of the scFvs referred to in Table 1 or any one of the recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that block or inhibit the ability of anthrax lethal toxin to kill cells or animals. In one embodiment, an antibody that blocks or inhibits the ability of anthrax lethal toxin to kill cells or animals comprises, or alternatively consists of a VH and/or a VL domain of at least one of the scFvs referred to in Table 1 or at least one of the recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1, or a fragment or variant thereof. In a specific embodiment, an antibody that blocks or inhibits the ability of anthrax lethal toxin to kill cells or animals comprises, or alternatively consists of a VH and a VL domain of any one of the scFvs referred to in Table 1 or any one of the recombinant antibodies expressed by the cell lines contained in the ATCC Deposits referred to in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

The present invention also provides for fusion proteins comprising, or alternatively consisting of, an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that specifically bind to PA fused to a heterologous polypeptide. Preferably, the heterologous polypeptide to which the antibody is fused is useful for function or is useful to target the fusion protein to cells with surface bound PA molecules. In specific embodi-

ments the invention encompasses bispecific antibodies in which one antibody binding site is specific for PA and the second antibody binding site is specific for a heterologous polypeptide. In one embodiment, a fusion protein of the invention comprises, or alternatively consists of, a polypeptide having the amino acid sequence of any one or more of the VH domains of an antibody of the invention or the amino acid sequence of any one or more of the VL domains of an antibody of the invention or fragments or variants thereof, and a heterologous polypeptide sequence. In another embodiment, a fusion protein of the present invention comprises, or alternatively consists of, a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs of an antibody of the invention, or the amino acid sequence of any one, two, three, or more of the VL CDRs of an antibody of the invention, or fragments or variants thereof, and a heterologous polypeptide sequence. In a preferred embodiment, the fusion protein comprises, or alternatively consists of, a polypeptide having the amino acid sequence of, a VH CDR3 of an antibody of the invention, or fragment or variant thereof, and a heterologous polypeptide sequence, which fusion protein specifically binds to PA. In another embodiment, a fusion protein comprises, or alternatively consists of a polypeptide having the amino acid sequence of at least one VH domain of an antibody of the invention and the amino acid sequence of at least one VL domain of an antibody of the invention or fragments or variants thereof, and a heterologous polypeptide sequence. Preferably, the VH and VL domains of the fusion protein correspond to a single antibody (or scFv or Fab fragment) of the invention. In yet another embodiment, a fusion protein of the invention comprises, or alternatively consists of a polypeptide having the amino acid sequence of any one, two, three or more of the VH CDRs of an antibody of the invention and the amino acid sequence of any one, two, three or more of the VL CDRs of an antibody of the invention, or fragments or variants thereof, and a heterologous polypeptide sequence. Preferably, two, three, four, five, six, or more of the VHCDR(s) or VLCDR(s) correspond to single antibody (or scFv or Fab fragment) of the invention. Nucleic acid molecules encoding these fusion proteins are also encompassed by the invention.

Antibodies of the present invention (including antibody fragments or variants thereof) may be characterized in a variety of ways. In particular, antibodies and related molecules of the invention may be assayed for the ability to specifically bind to PA or a fragment or variant of PA, using techniques described herein or routinely modifying techniques known in the art. Assays for the ability of the antibodies of the invention to specifically bind PA or a fragment or variant of PA, may be performed in solution (e.g., Houghten, *Bio/Techniques* 13:412-421 (1992)), on beads (e.g., Lam, *Nature* 354:82-84 (1991)), on chips (e.g., Fodor, *Nature* 364:555-556 (1993)), on bacteria (e.g., U.S. Pat. No. 5,223,409), on spores (e.g., U.S. Pat. Nos. 5,571,698; 5,403,484; and 5,223,409), on plasmids (e.g., Cull et al., *Proc. Natl. Acad. Sci. USA* 89:1865-1869 (1992)) or on phage (e.g., Scott and Smith, *Science* 249:386-390 (1990); Devlin, *Science* 249:404-406 (1990); Cwirla et al., *Proc. Natl. Acad. Sci. USA* 87:7178-7182 (1990); and Felici, *J. Mol. Biol.* 222:301-310 (1991)) (each of these references is incorporated herein in its entirety by reference). Antibodies that have been identified to specifically bind to PA or a fragment or variant of PA can then be assayed for their specificity and affinity for PA using or routinely modifying techniques described herein or otherwise known in the art (see, e.g., Examples 1 and 2).

The antibodies of the invention may be assayed for specific binding to PA polypeptides and cross-reactivity with other

antigens by any method known in the art. Immunoassays which can be used to analyze specific binding and cross-reactivity include, but are not limited to, competitive and non-competitive assay systems using techniques such as BIAcore analysis, FACS (fluorescence activated cell sorter) analysis, immunofluorescence, immunocytochemistry, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, western blots, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e.g., Ausubel et al., eds, 1994, *Current Protocols in Molecular Biology*, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

ELISAs comprise preparing antigen, coating the well of a 96-well microtiter plate with the antigen, washing away antigen that did not bind the wells, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) to the wells and incubating for a period of time, washing away unbound antibodies or non-specifically bound antibodies, and detecting the presence of the antibodies specifically bound to the antigen coating the well. In ELISAs, the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Alternatively, the antigen need not be directly coated to the well; instead the ELISA plates may be coated with an anti-Ig Fc antibody, and the antigen in the form of a PA-Fc fusion protein, may be bound to the anti-Ig Fc coated to the plate. This may be desirable so as to maintain the antigen protein (e.g., the PA polypeptides) in a more native conformation than it may have when it is directly coated to a plate. In another alternative, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, the detectable molecule could be the antigen conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase). One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Ausubel et al., eds, 1994, *Current Protocols in Molecular Biology*, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

The binding affinity of an antibody (including an scFv or other molecule comprising, or alternatively consisting of, antibody fragments or variants thereof) to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g., antigen labeled with ^3H or ^{125}I), or fragment or variant thereof with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of the present invention for PA and the binding off-rates can be determined from the data by Scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, a PA polypeptide is incubated with an antibody of the present invention conjugated to a labeled compound (e.g., compound labeled with ^3H or ^{125}I) in the presence of increasing amounts of an unlabeled second anti-PA antibody. Assays for determining the ability of one antibody to competitively

inhibit the binding of another antibody are known in the art (See, for example, Harlow, Ed & David Lane, *Antibodies: A Laboratory Manual*, New York: Cold Spring Harbor Laboratory, 1988. pp. 567-569.) This kind of competitive assay between two antibodies, may also be used to determine if two antibodies bind the same, closely associated (e.g., overlapping) or different epitopes.

In a preferred embodiment, BIAcore kinetic analysis is used to determine the binding on and off rates of antibodies (including antibody fragments or variants thereof) to PA, or fragments of PA.

Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40, or Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasyolol) supplemented with protein phosphatase and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1 to 4 hours) at 40 degrees C., adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 40 degrees C., washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e.g., pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, e.g., Ausubel et al., eds, 1994, *Current Protocols in Molecular Biology*, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%-20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e.g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e.g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e.g., an anti-human antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e.g., ^{32}P or ^{125}I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, e.g., Ausubel et al., eds, 1994, *Current Protocols in Molecular Biology*, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

Antibody Conjugates

The present invention encompasses antibodies (including antibody fragments or variants thereof), recombinantly fused or chemically conjugated (including both covalent and non-covalent conjugations) to a heterologous polypeptide (or portion thereof, preferably at least 10, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90 or at least 100 amino acids of the polypeptide) to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. For example, antibodies of the invention may be used to target heterologous

polypeptides to particular cell types (e.g., cancer cells), either in vitro or in vivo, by fusing or conjugating the heterologous polypeptides to antibodies of the invention that are specific for particular cell surface antigens or which bind antigens that bind particular cell surface receptors. Antibodies of the invention may also be fused to albumin (including but not limited to recombinant human serum albumin (see, e.g., U.S. Pat. No. 5,876,969, issued Mar. 2, 1999, EP Patent 0 413 622, and U.S. Pat. No. 5,766,883, issued Jun. 16, 1998, herein incorporated by reference in their entirety)), resulting in chimeric polypeptides. In a preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with the mature form of human serum albumin (i.e., amino acids 1-585 of human serum albumin as shown in FIGS. 1 and 2 of EP Patent 0 322 094) which is herein incorporated by reference in its entirety. In another preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with polypeptide fragments comprising, or alternatively consisting of, amino acid residues 1-z of human serum albumin, where z is an integer from 369 to 419, as described in U.S. Pat. No. 5,766,883 herein incorporated by reference in its entirety. Polypeptides and/or antibodies of the present invention (including fragments or variants thereof) may be fused to either the N- or C-terminal end of the heterologous protein (e.g., immunoglobulin Fc polypeptide or human serum albumin polypeptide). Polynucleotides encoding fusion proteins of the invention are also encompassed by the invention. Such fusion proteins may, for example, facilitate purification and may increase half-life in vivo. Antibodies fused or conjugated to heterologous polypeptides may also be used in in vitro immunoassays and purification methods using methods known in the art. See e.g., Harbor et al., supra, and PCT publication WO 93/2 1232; EP 439,095; Naramura et al., Immunol. Lett. 39:91-99 (1994); U.S. Pat. No. 5,474,981; Gillies et al., PNAS 89:1428-1432 (1992); Fell et al., J. Immunol. 146:2446-2452 (1991), which are incorporated by reference in their entireties.

The present invention further includes compositions comprising, or alternatively consisting of, heterologous polypeptides fused or conjugated to antibody fragments. For example, the heterologous polypeptides may be fused or conjugated to a Fab fragment, Fd fragment, Fv fragment, F(ab)₂ fragment, or a portion thereof. Methods for fusing or conjugating polypeptides to antibody portions are known in the art. See, e.g., U.S. Pat. Nos. 5,356,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 91/06570; Ashkenazi et al., Proc. Natl. Acad. Sci. USA 88: 10535-10539 (1991); Zheng et al., J. Immunol. 154:5590-5600 (1995); and Vil et al., Proc. Natl. Acad. Sci. USA 89:11357-11341 (1992) (said references incorporated by reference in their entireties).

Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to modulate the activities of antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), such methods can be used to generate antibodies with altered activity (e.g., antibodies with higher affinities and lower dissociation rates). See, generally, U.S. Pat. Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al., Curr. Opin. Biotechnol. 8:724-35 (1997); Harayama, Trends Biotechnol. 16(2):76-82 (1998); Hansson, et al., J. Mol. Biol. 287: 265-76 (1999); and Lorenzo and Blasco, Biotechniques 24(2):308-13 (1998) (each of these patents and publications

are hereby incorporated by reference in its entirety). In one embodiment, polynucleotides encoding antibodies of the invention may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more portions of a polynucleotide encoding an antibody which portions specifically bind to PA may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

Moreover, the antibodies of the present invention (including antibody fragments or variants thereof), can be fused to marker sequences, such as a polypeptides to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine polypeptide, such as the tag provided in a pQE vector (QLAGEN, Inc., 9259 Eton Avenue, Chatsworth, Calif., 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the hemagglutinin "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)) and the FLAG® tag (Stratagene, La Jolla, Calif.).

The present invention further encompasses antibodies (including antibody fragments or variants thereof), conjugated to a diagnostic or therapeutic agent. The antibodies can be used, for example, as part of a clinical testing procedure to, e.g., determine the safety or efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include, but are not limited to, various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Pat. No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include, but are not limited to, horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include, but are not limited to, streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include, but are not limited to, umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes, but is not limited to, luminol; examples of bioluminescent materials include, but are not limited to, luciferase, luciferin, and aequorin; and examples of suitable radioactive material include, but are not limited to, iodine (²¹¹I, ¹²³I, ¹²⁵I, ¹³¹I), carbon (¹⁴C), sulfur (³⁵S), tritium (³H), indium (¹¹¹In, ¹¹²In, ^{113m}In, ^{115m}In), technetium (⁹⁹Tc, ^{99m}Tc), thallium (²⁰¹Tl), gallium (⁶⁸Ga, ⁶⁷Ga), palladium (¹⁰³Pd), molybdenum (⁹⁹Mo), xenon (¹³⁵Xe), fluorine (¹⁸F), ¹⁵³Sm, ¹⁷⁷Lu, ¹⁵⁹Gd, ¹⁴⁹Pm, ¹⁴⁰La, ¹⁷⁵Yb, ¹⁶⁶Ho, ⁹⁰Y, ⁴⁷Sc, ¹⁸⁶Re, ⁸⁸Re, ¹⁴²Pr, ¹⁰⁵Rh, and ⁹⁷Ru.

Further, an antibody of the invention (including an scFv or other molecule comprising, or alternatively consisting of, antibody fragments or variants thereof), may be coupled or conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytotoxic agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example,

²¹³Bi, or other radioisotopes such as, for example, ¹⁰³Pd, ¹³⁵Xe, ¹³¹I, ⁶⁸Ge, ⁵⁷Co, ⁶⁵Zn, ⁸⁵Sr, ³²P, ³⁵S, ⁹⁰Y, ¹⁵³Sm, ¹⁵³Gd, ¹⁶⁹Yb, ⁵¹Cr, ⁵⁴Mn, ⁷⁵Se, ¹¹³Sn, ⁹⁰Y, ¹¹⁷Ti, ¹⁸⁶Re, ¹⁸⁸Re and ¹⁶⁶Ho. In specific embodiments, an antibody or fragment thereof is attached to macrocyclic chelators that chelate radiometal ions, including but not limited to, ¹⁷⁷Lu, ⁹⁰Y, ¹⁶⁶Ho, and ¹⁵³Sm, to polypeptides. In specific embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA). In other specific embodiments, the DOTA is attached to the an antibody of the invention or fragment thereof via a linker molecule. Examples of linker molecules useful for conjugating DOTA to a polypeptide are commonly known in the art—see, for example, DeNardo et al., *Clin Cancer Res.* 4(10):2483-90, 1998; Peterson et al., *Bioconjug. Chem.* 10(4):553-7, 1999; and Zimmerman et al., *Nucl. Med. Biol.* 26(8):943-50, 1999 which are hereby incorporated by reference in their entirety.

A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include, but are not limited to, paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, thymidine kinase, endonuclease, RNAse, and puromycin and fragments, variants or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

Techniques known in the art may be applied to label antibodies of the invention. Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Pat. Nos. 5,756,065; 5,714,711; 5,696,239; 5,652,371; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety) and direct coupling reactions (e.g., Bolton-Hunter and Chloramine-T reaction).

The antibodies of the invention which are conjugates can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, but are not limited to, for example, a toxin such as abrin, ricin A, alpha toxin, pseudomonas exotoxin, or diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin; a protein such as tumor necrosis factor, alpha-interferon, beta-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF-alpha, TNF-beta, AIM I (see, International Publication No. WO 97/35899), AIM II (see, International Publication No. WO 97/34911), Fas Ligand (Takahashi et al., *Int. Immunol.*, 6:1567-1574 (1994)), VEGF (see, International Publication No. WO 99/23105), a thrombotic agent or an anti-angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 (IL-1), interleukin-2

(IL-2), interleukin-6 (IL-6), granulocyte macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), or other growth factors.

Antibodies of the invention (including antibody fragments or variants thereof), may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

Techniques for conjugating a therapeutic moiety to antibodies are well known, see, e.g., Amon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.* 62:119-58 (1982).

Alternatively, an antibody of the invention can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Pat. No. 4,676,980, which is incorporated herein by reference in its entirety.

An antibody of the invention (including an other molecules comprising, or alternatively consisting of, an antibody fragment or variant thereof), with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

Uses of Antibodies of the Invention

Antibodies of the present invention may be used, for example, but not limited to, to purify, detect, and target the polypeptides of the present invention, including both in vitro and in vivo diagnostic and therapeutic methods. For example, the antibodies have use in immunoassays for qualitatively and quantitatively measuring levels of PA polypeptides in biological and non-biological samples. See, e.g., Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988) (incorporated by reference herein in its entirety). By way of another non-limiting example, antibodies of the invention may be administered to individuals as a form of passive immunization.

Prophylactic or therapeutic treatment with anti-PA antibodies has advantages over other anti-anthrax agents, such as antibiotics, in that anti-PA antibodies provide protection against drug resistant strains; anti-PA antibodies can be given as either a single dose treatment or can be given in multiple doses (e.g., bi-weekly or monthly dosing); individual doses of anti-PA antibodies will have a relatively long duration of effect; can be administered subcutaneously in addition to other routes of administration (e.g., intravenously), and will be useful in re-exposure or flare situations. Given that the anti-PA antibodies provided herein are fully human antibodies, the risk of side effects due to anti-PA treatment will be minimal when administered as fully human antibodies.

Epitope Mapping

The present invention provides antibodies (including antibody fragments or variants thereof), that can be used to identify epitopes of a PA polypeptide (e.g., SEQ ID NO:2) using

techniques described herein or otherwise known in the art. Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985), further described in U.S. Pat. No. 4,711,211.) Identified epitopes of antibodies of the present invention may, for example, be used as vaccine candidates, i.e., to immunize an individual to elicit antibodies against the naturally occurring forms of PA polypeptides.

Diagnostic Uses of Antibodies

Labeled antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) which specifically bind to a PA polypeptide can be used for diagnostic purposes to detect, diagnose, prognose, or monitor the presence of the intact *Bacillus anthracis* spore or organism, or simply the components of anthrax toxin. In specific embodiments, labeled antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) which specifically bind to a PA polypeptide can be used for diagnostic purposes to detect, diagnose, prognose, or monitor the course of anthrax infection.

The invention provides for the detection of expression of a PA polypeptide comprising: (a) assaying the expression of a PA polypeptide in a (biological—or non-biological) sample from an individual using one or more antibodies of the invention that specifically binds to PA; and (b) detecting the presence of PA polypeptide in the sample.

The invention provides for the detection of aberrant expression of a PA polypeptide comprising: (a) assaying the expression of a PA polypeptide in from one strain of *Bacillus anthracis* using one or more antibodies of the invention that specifically binds to PA; and (b) comparing the level of a PA polypeptide in the biological sample with a standard level of a PA polypeptide, e.g., in a reference strain of *Bacillus anthracis*, whereby an increase or decrease in the assayed level of a PA polypeptide compared to the standard level of a PA polypeptide is indicative of aberrant expression.

By "biological sample" is intended any fluids and/or cells obtained from an individual, body fluid, body tissue, body cell, cell line, tissue culture, bacterial culture, or other source which may contain a PA polypeptide protein or mRNA. Body fluids include, but are not limited to, sera, plasma, urine, synovial fluid, pleural fluid, edema fluid, spinal fluid, saliva, and mucous. Tissue samples may be taken from virtually any tissue in the body. Tissue samples may also be obtained from autopsy material. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

One aspect of the invention is the detection and diagnosis of a disease or disorder associated with *Bacillus anthracis* or anthrax toxins in an animal, preferably a mammal and most preferably a human.

Therapeutic and Prophylactic Uses of Antibodies

One or more antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that specifically bind to PA may be used locally or systemically in the body as a prophylactic or a therapeutic. The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) to an animal, preferably a mammal, and most preferably a human, for treating individuals infected with *Bacillus anthracis* bacteria and/or *B. anthracis* spores or individuals that have been exposed to *B. anthracis* bacteria,

B. anthracis spores and/or anthrax toxins. Anthrax infection occurs when an animal has *B. anthracis* bacteria and/or *B. anthracis* spores within its body or in contact with the surface of its body. An animal may be considered as poisoned with anthrax toxin when it has within its body or in contact with the surface of its body, lethal toxin, edema toxin, lethal factor or edema factor.

Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention and nucleic acids encoding antibodies of the invention as described herein. The treatment and/or prevention of anthrax infection and/or anthrax toxin poisoning includes alleviating or preventing symptoms associated with anthrax infection and/or anthrax toxin poisoning.

For example, bacteremia occurs in almost all cases of anthrax that progress to a fatal outcome. Antibodies of the invention may be used to prevent the development of bacteremia in anthrax patients or to treat patients that have developed bacteremia associated with anthrax infection. In specific embodiments, anti-PA antibodies of the invention which activate the complement cascade, i.e. IgG1, IgG2, IgG3, and IgA1 and IgM antibodies, are used to prevent the development of bacteremia in anthrax patients or to treat patients that have developed bacteremia associated with anthrax infection.

In other embodiments, antibodies of the invention may have a bactericidal and/or bacteriostatic effect on *B. anthracis* bacteria. By way of non-limiting example, antibodies of the invention may activate the classical complement pathway and/or enhance the activation of the alternative complement pathway. Alternatively, antibodies of the invention may opsonize *B. anthracis* bacteria. Opsonized bacteria then may be a target for antibody dependent cell-mediated cytotoxicity (ADCC). In another embodiment, antibodies of the invention may catalyze the generation of hydrogen peroxide from singlet molecular oxygen and water which chemical reaction results in the efficient killing of bacteria. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

Therapeutic/Prophylactic Compositions and Administration

The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of antibody (or fragment or variant thereof) or pharmaceutical composition of the invention, preferably an antibody of the invention. In a preferred aspect, an antibody or fragment or variant thereof is substantially purified (i.e., substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to, animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably a human.

Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

Various delivery systems are known and can be used to administer antibody or fragment or variant thereof of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the antibody or antibody fragment, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432

(1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

The preferred route of administration for antibodies of the invention will depend, in part, on the time of administration relative to the time of exposure or potential exposure to anthrax bacterium, anthrax spores, and/or anthrax derived toxins such as lethal toxin and edema toxin. For example, if administration of the antibody to an individual occurs after an actual or suspected exposure to anthrax bacterium, anthrax spores, and/or anthrax derived toxins, it would be most expedient to deliver the antibodies via a route which will provide the quickest time to maximum concentration (T_{max}) and/or the greatest maximum concentration (C_{max}) of serum anti-PA antibody levels. The shortest T_{max} in serum is achieved using intravenous administration, because the antibody is delivered directly to the serum. It has also been shown in pharmacokinetic studies using rabbits and cynomolgus monkeys, that intramuscular administration results in a slightly higher C_{max} and a slightly faster T_{max} as compared to subcutaneous administration. Thus, post-exposure administration of antibodies of the invention is preferably performed intravenously. However, due to the time, materials and facilities required for intravenous administration, other routes of administration (such as intramuscular or subcutaneous administration) may be preferable for post-exposure administration of anti-PA antibodies especially in mass exposure events, exposure events in isolated areas or in battlefield conditions, or other similar situations.

On the other hand, if the time the antibody stays in the body (residence time) is the greatest clinical consideration, it may be preferable to administer the antibody via a route that provides for a relatively long terminal half life of the antibody in serum and a long residence time. If antibodies are being administered prophylactically, prior to exposure or potential exposure to anthrax bacterium, anthrax spores, and/or anthrax derived toxins, it would be desirable to ensure the greatest longevity of the efficacy of the prophylactic antibody treatment by administering the antibodies via the route that provides for a relatively long terminal half life of the antibody in serum and a long residence time. It has been shown in pharmacokinetic studies using rabbits and cynomolgus monkeys, that that intramuscular or subcutaneous administration gives a longer terminal half life and/or residence time compared to intravenous administration. Thus, pre-exposure administration of anti-PA antibodies of the invention is preferably performed intramuscularly or subcutaneously.

In a preferred embodiment the antibody of the invention is formulated in 10 mM sodium citrate, 1.8% glycine, 1.0% sucrose, 0.02% polysorbate 80 (w/v), pH 6.5. In another preferred embodiment, the antibody of the invention is formulated in 10 mM sodium citrate, 1.8% glycine, 1.0%

sucrose, 0.02% polysorbate 80 (w/v), pH 6.5 for subcutaneous, intramuscular and/or intravenous administration. Of course, any formulation suitable for clinical administration may be used.

In a specific embodiment, it may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

In another embodiment, the composition can be delivered in a vesicle, in particular a liposome (see Langer, *Science* 249:1527-1535 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*).

In yet another embodiment, the composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, *CRC Crit. Rev. Biomed. Eng.* 14:201 (1987); Buchwald et al., *Surgery* 88:507 (1980); Saudek et al., *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used (see *Medical Applications of Controlled Release*, Langer and Wise (eds.), CRC Press, Boca Raton, Fla. (1974); *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., *Macromol. Sci. Rev. Macromol. Chem.* 23:71 (1983); see also Levy et al., *Science* 228:190 (1985); During et al., *Ann. Neurol.* 25:351 (1989); Howard et al., *J. Neurosurg.* 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in *Medical Applications of Controlled Release*, *supra*, vol. 2, pp. 115-138 (1984)).

Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1535 (1990)).

In a specific embodiment where the composition of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered *in vivo* to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Pat. No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (see e.g., Joliet et al., *Proc. Natl. Acad. Sci. USA* 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of an antibody or a fragment thereof, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent,

adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin. Such compositions will contain a therapeutically effective amount of the antibody or fragment thereof, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration, are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

The compositions of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The amount of the composition of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each

patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 50 mg/kg of the patient's body weight. In specific embodiments, the dosage administered to a patient is exactly or about 1 mg/kg of the patient's body weight. In specific embodiments, the dosage administered to a patient is exactly or about 3 mg/kg of the patient's body weight. In specific embodiments, the dosage administered to a patient is exactly or about 5 mg/kg of the patient's body weight. In specific embodiments, the dosage administered to a patient is exactly or about 10 mg/kg of the patient's body weight. In specific embodiments, the dosage administered to a patient is exactly or about 20 mg/kg of the patient's body weight. In specific embodiments, the dosage administered to a patient is exactly or about 30 mg/kg of the patient's body weight. In specific embodiments, the dosage administered to a patient is exactly or about 40 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of therapeutic or pharmaceutical compositions of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by modifications such as, for example, lipidation.

Because bacteria and/or toxin will already be present when a patient is to be treated therapeutically, therapeutic dosages generally will be greater than prophylactic dosages. In specific embodiments, a therapeutic dosage of anti-PA antibodies of the invention will be in the range of 1 to 100 mg/kg of the patient's body weight. In preferred embodiments, a therapeutic dosage of anti-PA antibodies of the invention will be in the range of 10 to 40 mg/kg of the patient's body weight. In specific preferred embodiments, a therapeutic dosage of anti-PA antibodies of the invention will be exactly or about 10 mg/kg of the patient's body weight. In specific preferred embodiments, a therapeutic dosage of anti-PA antibodies of the invention will be exactly or about 20 mg/kg of the patient's body weight. In specific preferred embodiments, a therapeutic dosage of anti-PA antibodies of the invention will be exactly or about 30 mg/kg of the patient's body weight. In specific preferred embodiments, a therapeutic dosage of anti-PA antibodies of the invention will be exactly or about 40 mg/kg of the patient's body weight.

In specific embodiments, a prophylactic dose of anti-PA antibodies of the invention will be in the range of 0.1 to 20 mg/kg of the patient's body weight. In preferred embodiments, a prophylactic dose of anti-PA antibodies of the invention will be in the range of 1 to 10 mg/kg of the patient's body weight. In specific preferred embodiments, a prophylactic dose of anti-PA antibodies of the invention will be exactly or about 1 mg/kg of the patient's body weight. In specific preferred embodiments, a prophylactic dose of anti-PA antibodies of the invention will be exactly or about 3 mg/kg of the patient's body weight. In specific preferred embodiments, a prophylactic dose of anti-PA antibodies of the invention will be exactly or about 5 mg/kg of the patient's body weight. In specific preferred embodiments, a prophylactic dose of anti-PA antibodies of the invention will be exactly or about 10 mg/kg of the patient's body weight.

Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same

species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments, or variants, (e.g., derivatives), or nucleic acids, are administered to a human patient for therapy or prophylaxis.

It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that specifically bind to PA, or polynucleotides encoding antibodies that specifically bind to PA, for both immunoassays and administration to patients. Such antibodies will preferably have an affinity for PA and/or PA polypeptide fragments. Preferred binding affinities include those with a dissociation constant or K_D of less than or equal to 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, or 10^{-5} M. More preferably, antibodies of the invention bind PA polypeptides or fragments or variants thereof with a dissociation constant or K_D less than or equal to 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, or 10^{-8} M. Even more preferably, antibodies of the invention bind PA polypeptides or fragments or variants thereof with a dissociation constant or K_D less than or equal to 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, or 10^{-15} M.

As discussed in more detail below, the antibodies of the present invention may be used either alone or in combination with other compositions. The antibodies may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalent and non-covalent conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Pat. No. 5,314,995; and EP 396,387.

The antibody and antibody compositions of the invention may be administered alone or in combination with other therapeutic agents, including but not limited to antibiotics, antivirals, anti-retroviral agents, steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic agents and cytokines. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

In some embodiments, antibodies of the invention that are administered to an animal, preferably a human, for therapeutic or prophylactic uses are multimeric antibodies. In specific embodiments, antibodies of the invention are homodimeric IgG molecules. In other specific embodiments, antibodies of the invention are homodimeric IgG1 molecules. In specific embodiments, antibodies of the invention are homotrimeric IgG molecules. In other specific embodiments, antibodies of the invention are trimeric IgG1 molecules. In other specific embodiments, antibodies of the invention are higher-order multimers of IgG molecules (e.g., tetramers, pentamers and hexamers). In still further specific embodiments, antibodies of the IgG molecules comprising the higher order multimers of IgG molecules are IgG1 molecules.

Alternatively, antibodies of the invention for therapeutic or prophylactic uses may be administered in combination with crosslinking agents known in the art, including but not limited to anti-IgG antibodies.

5 Combination Administration with Antibiotics, Other Anti-Anthrax Agents, or Other Anti-Bioterrorism Agents

The antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be administered alone or in combination with other therapeutic or prophylactic regimens (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy, anti-tumor agents, anti-angiogenesis and anti-inflammatory agents). In specific embodiments, antibodies of the invention are administered in combination with one or more anti-anthrax agents. An anti-anthrax agent is a substance that is used to treat or prevent anthrax infection and/or anthrax toxin-poisoning. Such combinatorial therapy may be administered sequentially and/or concomitantly.

The antibodies of the invention may be administered prophylactically or therapeutically. It is specifically contemplated that the antibodies of the invention may be administered to provide protection against anthrax infection and/or anthrax toxin exposure as a supplementary or supportive measure in addition to other prophylactic or therapeutic regimens. For example, conventional treatment for known or suspected anthrax infection and/or anthrax toxin exposure typically includes immunization with an anthrax vaccine and/or administration of antibiotics. However, it takes significant time both for an individual or animal to build up antibody titers against anthrax following immunization, and for antibiotic treatment regimens to effectively control an anthrax infection. During these time periods, conventional treatment does little to offset the clinical effect of anthrax toxins on the patient. In one embodiment of the invention, the antibodies of the invention may be administered as a form of passive immunization or supportive therapy during the time period following immunization with an anthrax vaccine, in order to prevent or lessen the effect of anthrax toxins prior to development of protective levels of anti-anthrax antibody titers. Another exemplary use of the antibodies of the invention is as supportive or supplemental therapy for an individual undergoing antibiotic treatment for anthrax exposure, in order to prevent or lessen the effect of anthrax toxins while the antibiotic treatment regimen is given time to eliminate the anthrax infection.

In specific embodiments, anti-PA antibodies of the invention may be administered in combination with other anti-PA antibodies, or other antibodies reactive with different protein components of *Bacillus anthracis* or anthrax toxin components (including EF and LF).

In specific embodiments, anti-PA antibodies of the invention may be administered in combination with one or more antibiotic agents. In a particular embodiment, anti-PA antibodies of the invention may be administered in combination with the antibiotic Ciprofloxacin Hydrochloride (Cipro). In other embodiments, anti-PA antibodies of the invention may be administered in combination with the antibiotic doxycycline. In other embodiments, anti-PA antibodies of the invention may be administered in combination with the antibiotic penicillin G procaine. In other embodiments, anti-PA antibodies of the invention may be administered in combination with the antibiotic amoxicillin. In other embodiments, anti-PA antibodies of the invention may be administered in combination with the antibiotic ofloxacin. In other embodiments, anti-PA antibodies of the invention may be administered in combination with the antibiotic penicillin levofloxacin.

Other antibiotics that may be administered in combination with anti-PA antibodies of the invention include, but are not limited to, aminoglycosides, beta-lactam (glycopeptide), beta-lactamases, Clindamycin, chloramphenicol, cephalosporins, erythromycin, fluoroquinolones, macrolides, metronidazole, cephalothin, cefazolin, penicillins, quinolones, rifampin, streptomycin, sulfonamide, tetracyclines, imipenem, clarithromycin, gentamycin, and vancomycin.

In specific embodiments, antibodies of the invention are administered in combination with other therapeutics or prophylactics such as a soluble form of an anthrax receptor (e.g., SEQ ID NO:3 described in Nature (2002) 414:225-229 which is hereby incorporated by reference in its entirety, e.g., a polypeptide comprising amino acids 1 to 227 of 41-227 SEQ ID NO:3), a soluble form of the CMG2 receptor (described in Scobie et al., *Proceedings of the National Academy of Sciences USA* (2003) 100:5170-5174 which is hereby incorporated by reference in its entirety) or anti-ATR or anti-CMG2 antibodies that block binding of PA to ATR or CMG2, respectively. Other therapeutics or prophylactics that may be administered in combination with an antibody of the present invention include mutant forms of PA such as the EF/LF translocation deficient forms of PA described in International Publication Number WO01/82788 and in Science (2001) 292:695-697, both of which are hereby incorporated by reference in their entireties. Other therapeutics or prophylactics that may be administered in combination with an antibody of the present invention include peptide inhibitors that block LF binding to PA such as the P1 peptide, or its polyvalent form described in Nature Biotechnology (2002) 19:958-961 which is hereby incorporated by reference in its entirety. Still other therapeutics or prophylactics that may be administered in combination with an antibody of the present invention include, but are not limited to antibiotics, anthrax vaccines, antibodies immunoreactive with LF, EF or other protein moieties of *Bacillus anthracis*.

In specific embodiments, antibodies of the invention are administered in combination with anthrax vaccines, including but not limited to vaccines such as Anthrax Vaccine Adsorbed (AVA, also known as MDPH-PA and BioThrax), manufactured by BioPort Corporation, Lansing, Mich.; the vaccine manufactured by the Center for Applied Microbiology & Research (CAMR), Porton Down, Salisbury, England; vaccines utilizing recombinantly expressed anthrax PA, LF and/or EF proteins, whether wild-type or mutated (including both naturally occurring and artificially generated mutants); and other anthrax vaccines, including live, modified live, and killed vaccines.

In another specific embodiment, antibodies and antibody compositions of the invention are administered in combination with protease inhibitors. In specific embodiments, antibodies and antibody compositions of the invention are administered in combination with furin inhibitors.

Additional Combination Therapies

In other embodiments, antibody and antibody compositions of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the antibody and antibody compositions of the invention, include, but are not limited to, dapsone, pentamidine, atovaquone, isoniazid, rifampin, pyrazinamide, ethambutol, rifabutin, clarithromycin, azithromycin, ganciclovir, foscarnet, cidofovir, fluconazole, itraconazole, ketoconazole, acyclovir, famciclovir, pyrimethamine, leucovorin, NEUPOGENTTM (filgrastim/G-CSF), and LEUKINETM (sargramostim/GM-CSF). In a specific embodiment, anti-

body and antibody compositions of the invention are used in any combination with trimethoprim-sulfamethoxazole, dasone, pentamidine, and/or atovaquone to prophylactically treat, prevent, and/or diagnose an opportunistic *Pneumocystis carinii* pneumonia infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with isoniazid, rifampin, pyrazinamide, and/or ethambutol to prophylactically treat, prevent, and/or diagnose an opportunistic *Mycobacterium avium* complex infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with rifabutin, clarithromycin, and/or azithromycin to prophylactically treat, prevent, and/or diagnose an opportunistic *Mycobacterium tuberculosis* infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with ganciclovir, foscarnet, and/or cidofovir to prophylactically treat, prevent, and/or diagnose an opportunistic cytomegalovirus infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with fluconazole, itraconazole, and/or ketoconazole to prophylactically treat, prevent, and/or diagnose an opportunistic fungal infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with acyclovir and/or famciclovir to prophylactically treat, prevent, and/or diagnose an opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with pyrimethamine and/or leucovorin to prophylactically treat, prevent, and/or diagnose an opportunistic *Toxoplasma gondii* infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with leucovorin and/or NEUPOGENTTM (filgrastim/G-CSF) to prophylactically treat, prevent, and/or diagnose an opportunistic bacterial infection.

In a further embodiment, the antibody and antibody compositions of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, acyclovir, ribavirin, amantadine, and remantidine.

In certain embodiments, Therapeutics of the invention are administered in combination with antiretroviral agents, nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and/or protease inhibitors (PIs). NRTIs that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, RETROVIRTM (zidovudine/AZT), VIDEXTTM (didanosine/ddI), HIVIDTM (zalcitabine/ddC), ZERITTM (stavudine/d4T), EPIVIRTM (lamivudine/3TC), and COMBIVIRTM (zidovudine/lamivudine). NNRTIs that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, VIRAMUNETM (nevirapine), RESCRIPTORTM (delavirdine), and SUSTIVATM (efavirenz). Protease inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, CRIVANTM (indinavir), NORVIRTM (ritonavir), INVIRASETM (saquinavir), and VIRACEPTTM (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in any combination with Therapeutics of the invention to treat AIDS and/or to prevent or treat HIV infection.

In a specific embodiment, compositions of the invention are administered in combination with a chemotherapeutic

agent. Chemotherapeutic agents that may be administered with the compositions of the invention include, but are not limited to, antibiotic derivatives (e.g., doxorubicin (adriamycin), bleomycin, daunorubicin, and dactinomycin); antiestrogens (e.g., tamoxifen); antimetabolites (e.g., fluorouracil, 5-FU, methotrexate, floxuridine, interferon alpha-2b, glutamic acid, plicamycin, mercaptopurine, and 6-thioguanine); cytotoxic agents (e.g., carmustine, BCNU, lomustine, CCNU, cytosine arabinoside, cyclophosphamide, estramustine, hydroxyurea, procarbazine, mitomycin, busulfan, cisplatin, and vincristine sulfate); hormones (e.g., medroxyprogesterone, estramustine phosphate sodium, ethinyl estradiol, estradiol, megestrol acetate, methyltestosterone, diethylstilbestrol diphosphate, chlorotrianisene, and testolactone); nitrogen mustard derivatives (e.g., mephallen, chorambucil, mechlorethamine (nitrogen mustard) and thiotepea); steroids and combinations (e.g., bethamethasone sodium phosphate); and others (e.g., dicarbazine, asparaginase, mitotane, vincristine sulfate, vinblastine sulfate, etoposide, Topotecan, 5-Fluorouracil, paclitaxel (Taxol), Cisplatin, Cytarabine, and IFN-gamma, irinotecan (Camptosar, CPT-11), irinotecan analogs, and gemcitabine (GEMZAR™)).

In a specific embodiment, antibody and antibody compositions of the invention are administered in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or any combination of the components of CHOP. In another embodiment, antibody and antibody compositions of the invention are administered in combination with Rituximab. In a further embodiment, antibody and antibody compositions of the invention are administered with Rituximab and CHOP, or Rituximab and any combination of the components of CHOP.

In additional preferred embodiments, the compositions of the invention are administered in combination with TRAIL polypeptides or fragments or variants thereof, particularly of the extracellular soluble domain of TRAIL.

In one embodiment, the compositions of the invention are administered in combination with other members of the TNF family or antibodies specific for TNF receptor family members. In specific embodiments antibodies and antibody compositions of the invention are administered in combination with anti-TNF-alpha and/or anti-IL-1Beta antibodies. TNF, TNF-related or TNF-like molecules that may be administered with the compositions of the invention include, but are not limited to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), TRAIL, AIM-II (International Publication No. WO 97/34911), APRIL (J. Exp. Med. 188(6):1185-1190), endokine-alpha (International Publication No. WO 98/07880), TR6 (International Publication No. WO 98/30694), OPG, and neutrokin-alpha (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-1BB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/35904), TR5 (International Publication No. WO 98/30693), TR6 (International Publication No. WO 98/30694), TR7 (International Publication No. WO 98/41629), TRANK, TR9 (International Publication No. WO 98/56892), TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

In a more preferred embodiment, the antibody and antibody compositions of the invention are administered in com-

bination with an antimalarial, methotrexate, anti-TNF antibody, ENBREL™ (etanercept) and/or sufasalazine. In one embodiment, the antibody and antibody compositions of the invention are administered in combination with methotrexate. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with anti-TNF antibody. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with methotrexate and anti-TNF antibody. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with sufasalazine. In another specific embodiment, the antibody and antibody compositions of the invention are administered in combination with methotrexate, anti-TNF antibody, and sufasalazine. In another embodiment, the antibody and antibody compositions of the invention are administered in combination ENBREL™ (etanercept). In another embodiment, the antibody and antibody compositions of the invention are administered in combination with ENBREL™ (etanercept) and methotrexate. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with ENBREL™ (etanercept), methotrexate and sufasalazine. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with ENBREL™ (etanercept), methotrexate and sufasalazine. In other embodiments, one or more antimalarials is combined with one of the above-recited combinations. In a specific embodiment, the antibody and antibody compositions of the invention are administered in combination with an antimalarial (e.g., hydroxychloroquine), ENBREL™ (etanercept), methotrexate and sufasalazine. In another specific embodiment, the antibody and antibody compositions of the invention are administered in combination with an antimalarial (e.g., hydroxychloroquine), sufasalazine, anti-TNF antibody, and methotrexate.

Conventional nonspecific immunosuppressive agents, that may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs cyclophosphamide, cyclophosphamide IV, methylprednisolone, prednisolone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells.

In specific embodiments, antibody and antibody compositions of the invention are administered in combination with immunosuppressants. Immunosuppressants preparations that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, ORTHOCLONE™ (OKT3), SANDIMMUNE™/NEORAL™/SANGDYA™ (cyclosporin), PROGRAFT™ (tacrolimus), CELLCEPT™ (mycophenolate), Azathioprine, glucocorticosteroids, and RAPAMUN™ (sirolimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with steroid therapy. Steroids that may be administered in combination with the antibody and antibody compositions of the invention, include, but are not limited to, oral corticosteroids, prednisone, and methylprednisolone (e.g., IV methylprednisolone). In a specific embodiment, antibody and antibody compositions of the invention are administered in combination with prednisone. In a further specific embodiment, the antibody and antibody compositions of the invention are administered in combination with prednisone and an immunosuppressive agent. Immunosuppressive agents that may be administered with the antibody and antibody compo-

sitions of the invention and prednisone are those described herein, and include, but are not limited to, azathioprine, cyclophosphamide, and cyclophosphamide IV. In another specific embodiment, antibody and antibody compositions of the invention are administered in combination with methylprednisolone. In a further specific embodiment, the antibody and antibody compositions of the invention are administered in combination with methylprednisolone and an immunosuppressive agent. Immunosuppressive agents that may be administered with the antibody and antibody compositions of the invention and methylprednisolone are those described herein, and include, but are not limited to, azathioprine, cyclophosphamide, and cyclophosphamide IV.

The invention also encompasses combining the polynucleotides and/or polypeptides of the invention (and/or agonists or antagonists thereof) with other proposed or conventional hematopoietic therapies. Thus, for example, the polynucleotides and/or polypeptides of the invention (and/or agonists or antagonists thereof) can be combined with compounds that singly exhibit erythropoietic stimulatory effects, such as erythropoietin, testosterone, progenitor cell stimulators, insulin-like growth factor, prostaglandins, serotonin, cyclic AMP, prolactin, and triiodothyronine. Also encompassed are combinations of the antibody and antibody compositions of the invention with compounds generally used to treat aplastic anemia, such as, for example, methenolene, stanozolol, and nandrolone; to treat iron-deficiency anemia, such as, for example, iron preparations; to treat malignant anemia, such as, for example, vitamin B₁₂ and/or folic acid; and to treat hemolytic anemia, such as, for example, adrenocortical steroids, e.g., corticoids. See e.g., Resegotti et al., *Panminerva Medica*, 23:243-248 (1981); Kurtz, *FEBS Letters*, 14a:105-108 (1982); McGonigle et al., *Kidney Int.*, 25:437-444 (1984); and Pavlovic-Kantera, *Expt. Hematol.*, 8(supp. 8) 283-291 (1980), the contents of each of which are hereby incorporated by reference in their entireties.

Compounds that enhance the effects of or synergize with erythropoietin are also useful as adjuvants herein, and include but are not limited to, adrenergic agonists, thyroid hormones, androgens, hepatic erythropoietic factors, erythropoietins, and erythroginins. See for e.g., Dunn, "Current Concepts in Erythropoiesis", John Wiley and Sons (Chichester, England, 1983); Kalmani, *Kidney Int.*, 22:383-391 (1982); Shahidi, *New Eng. J. Med.*, 289:72-80 (1973); Urabe et al., *J. Exp. Med.*, 149:1314-1325 (1979); Billat et al., *Expt. Hematol.*, 10:135-140 (1982); Naughton et al., *Acta Haemat.*, 69:171-179 (1983); Cognote et al. in abstract 364, *Proceedings 7th Intl. Cong. of Endocrinology* (Quebec City, Quebec, Jul. 1-7, 1984); and Rothman et al., 1982, *J. Surg. Oncol.*, 20:105-108 (1982). Methods for stimulating hematopoiesis comprise administering a hematopoietically effective amount (i.e., an amount which effects the formation of blood cells) of a pharmaceutical composition containing polynucleotides and/or polypeptides of the invention to a patient. The polynucleotides and/or polypeptides of the invention are administered to the patient by any suitable technique, including but not limited to, parenteral, sublingual, topical, intrapulmonary and intranasal, and those techniques further discussed herein. The pharmaceutical composition optionally contains one or more members of the group consisting of erythropoietin, testosterone, progenitor cell stimulators, insulin-like growth factor, prostaglandins, serotonin, cyclic AMP, prolactin, triiodothyronine, methenolene, stanozolol, and nandrolone, iron preparations, vitamin B₁₂, folic acid and/or adrenocortical steroids.

In an additional embodiment, the antibody and antibody compositions of the invention are administered in combina-

tion with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, LEUKINE™ (sargramostim/GM-CSF) and NEUPOGEN™ (filgrastim/G-CSF).

In an additional embodiment, the antibody and antibody compositions of the invention are administered alone or in combination with an anti-angiogenic agent(s). Anti-angiogenic agents that may be administered with the antibody and antibody compositions of the invention include, but are not limited to; Angiostatin (Entremed, Rockville, Md.), Tropolin-1 (Boston Life Sciences, Boston, Mass.), anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel (Taxol), Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, VEG1, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include, but are not limited to, platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., *Cancer Res.* 51:22-26, 1991); Sulphated Polysaccharide Peptidoglycan Complex (SP-PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha, alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., *J. Bio. Chem.* 267:17321-17326, 1992); Chymostatin (Tomkinson et al., *Biochem J.* 286:475-480, 1992); Cystodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin. (Ingber et al., *Nature* 348:555-557, 1990); Gold

Sodium Thiomaleate ("GST"; Matsubara and Ziff, *J. Clin. Invest.* 79:1440-1446, 1987); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., *J. Biol. Chem.* 262(4):1659-1664, 1987); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2-carboxyphenyl)-4-chloroanthronilic acid disodium or "CCA"; (Takeuchi et al., *Agents Actions* 36:312-316, 1992); and metalloproteinase inhibitors such as BB94.

Additional anti-angiogenic factors that may also be utilized within the context of the present invention include Thalidomide, (Celgene, Warren, N.J.); Angiostatic steroid; AGM-1470 (H. Brem and J. Folkman *J. Pediatr. Surg.* 28:445-51 (1993)); an integrin alpha v beta 3 antagonist (C. Storgard et al., *J. Clin. Invest.* 103:47-54 (1999)); carboxynaminolimidazole; Carboxyamidotriazole (CAI) (National Cancer Institute, Bethesda, Md.); Conbretastatin A-4 (CA4P) (OXIGENE, Boston, Mass.); Squalamine (Magainin Pharmaceuticals, Plymouth Meeting, Pa.); TNP-470, (Tap Pharmaceuticals, Deerfield, Ill.); ZD-0101 AstraZeneca (London, UK); APRA (CT2584); Benefin, Byrostatin-1 (SC359555); CGP-41251 (PKC 412); CM101; Dexrazoxane (ICRF187); DMXAA; Endostatin; Flavopridiol; Genestein; GTE; InmTher; Iressa (ZD1839); Octreotide (Somatostatin); Pan-retin; Penacillamine; Photopoint; PI-88; Prinomastat (AG-3540) Purlytin; Suradista (FCE26644); Tamoxifen (Nolvadex); Tazarotene; Tetrathiomolybdate; Xeloda (Capecitabine); and 5-Fluorouracil.

Anti-angiogenic agents that may be administered in combination with the compounds of the invention may work through a variety of mechanisms including, but not limited to, inhibiting proteolysis of the extracellular matrix, blocking the function of endothelial cell-extracellular matrix adhesion molecules, by antagonizing the function of angiogenesis inducers such as growth factors, and inhibiting integrin receptors expressed on proliferating endothelial cells. Examples of anti-angiogenic inhibitors that interfere with extracellular matrix proteolysis and which may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, AG-3540 (Agouron, La Jolla, Calif.), BAY-12-9566 (Bayer, West Haven, Conn.), BMS-275291 (Bristol Myers Squibb, Princeton, N.J.), CGS-27032A (Novartis, East Hanover, N.J.), Marimastat (British Biotech, Oxford, UK), and Metastat (Aeterna, St-Foy, Quebec). Examples of anti-angiogenic inhibitors that act by blocking the function of endothelial cell-extracellular matrix adhesion molecules and which may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, EMD-121974 (Merck KgaA Darmstadt, Germany) and Vitaxin (IXsys, La Jolla, Calif./Medimmune, Gaithersburg, Md.). Examples of anti-angiogenic agents that act by directly antagonizing or inhibiting angiogenesis inducers and which may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, Angiozyme (Ribozyme, Boulder, Colo.), Anti-VEGF antibody (Genentech, S. San Francisco, Calif.), PTK-787/ZK-225846 (Novartis, Basel, Switzerland), SU-101 (Sugen, S. San Francisco, Calif.), SU-5416 (Sugen/Pharmacia Upjohn, Bridgewater, N.J.), and SU-6668 (Sugen). Other anti-angiogenic agents act to indirectly inhibit angiogenesis. Examples of indirect inhibitors of angiogenesis which may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, IM-862 (Cytran, Kirkland, Wash.), Interferon-alpha, IL-12 (Roche, Nutley, N.J.), and Pentosan polysulfate (Georgetown University, Washington, D.C.).

In particular embodiments, the use of antibody and antibody compositions of the invention in combination with anti-

angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of cancers and other hyperproliferative disorders.

In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with CD40 ligand (CD40L), a soluble form of CD40L (e.g., avrend), biologically active fragments, variants, or derivatives of CD40L, anti-CD40L antibodies (e.g., agonistic or antagonistic antibodies), and/or anti-CD40 antibodies (e.g., agonistic or antagonistic antibodies).

In another embodiment, antibody and antibody compositions of the invention are administered in combination with an anticoagulant. Anticoagulants that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, heparin, warfarin, and aspirin. In a specific embodiment, antibody and antibody compositions of the invention are administered in combination with heparin and/or warfarin. In another specific embodiment, antibody and antibody compositions of the invention are administered in combination with warfarin and aspirin. In another specific embodiment, antibody and antibody compositions of the invention are administered in combination with heparin. In another specific embodiment, antibody and antibody compositions of the invention are administered in combination with heparin and aspirin.

In another embodiment, antibody and antibody compositions of the invention are administered in combination with an agent that suppresses the production of anticardiolipin antibodies. In specific embodiments, the polynucleotides of the invention are administered in combination with an agent that blocks and/or reduces the ability of anticardiolipin antibodies to bind phospholipid-binding plasma protein beta 2-glycoprotein I (b2GPI).

In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with an antimalarial. Antimalarials that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, hydroxychloroquine, chloroquine, and/or quinacrine.

In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with an NSAID.

In a nonexclusive embodiment, the antibody and antibody compositions of the invention are administered in combination with one, two, three, four, five, ten, or more of the following drugs: NRD-101 (Hoechst Marion Roussel), diclofenac (Dimethaid), oxaprozin potassium (Monsanto), mecasemin (Chiron), T-714 (Toyama), pemetrexed disodium (Eli Lilly), atreleuton (Abbott), valdecoxib (Monsanto), eltenac (Byk Gulden), campath, AGM-1470 (Takeda), CDP-571 (Celltech Chiroscience), CM-101 (CarboMed), ML-3000 (Merckle), CB-2431 (KS Biomedix), CBF-BS2 (KS Biomedix), IL-1Ra gene therapy (Valentis), JTE-522 (Japan Tobacco), paclitaxel (Angiotech), DW-1166HC (Dong Wha), darbufelone mesylate (Warner-Lambert), soluble TNF receptor 1 (synergen; Amgen), IPR-6001 (Institute for Pharmaceutical Research), trocade (Hoffman-La Roche), EF-5 (Scotia Pharmaceuticals), BIIL-284 (Boehringer Ingelheim), BILF-1149 (Boehringer Ingelheim), LeukoVax (Inflammatics), MK-671 (Merck), ST-1482 (Sigma-Tau), and butixocort propionate (WarnerLambert).

In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with one, two, three, four, five or more of the following drugs: methotrexate, sulfasalazine, sodium aurothiomalate,

auranofin, cyclosporine, penicillamine, azathioprine, an anti-malarial drug (e.g., as described herein), cyclophosphamide, chlorambucil, gold, ENBREL™ (Etanercept), anti-TNF antibody, LJP 394 (La Jolla Pharmaceutical Company, San Diego, Calif.) and prednisolone.

In an additional embodiment, antibody and antibody compositions of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the antibody and antibody compositions of the invention include, but not limited to, GAMMART™ (immune serum globulin), IVEEGAM™ (immune serum globulin), SANDOglobulin™ (immune globulin), GAMMAGARD S/D™ (immunoglobulin), and GAMIMUNET™ (immune serum globulin). In a specific embodiment, antibody and antibody compositions of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

CD40 ligand (CD40L), a soluble form of CD40L (e.g., avrend), biologically active fragments, variants, or derivatives of CD40L, anti-CD40L antibodies (e.g., agonistic or antagonistic antibodies), and/or anti-CD40 antibodies (e.g., agonistic or antagonistic antibodies).

In an additional embodiment, the antibody and antibody compositions of the invention are administered in combination with cytokines. Cytokines that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, GM-CSF, G-CSF, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-alpha, IFN-beta, IFN-gamma, TNF-alpha, and TNF-beta. In preferred embodiments, antibody and antibody compositions of the invention are administered with TRAIL receptor. In another embodiment, antibody and antibody compositions of the invention may be administered with any interleukin, including, but not limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, IL-21, and IL-22. In preferred embodiments, the antibody and antibody compositions of the invention are administered in combination with IL4 and IL10.

In one embodiment, the antibody and antibody compositions of the invention are administered in combination with one or more chemokines. In specific embodiments, the antibody and antibody compositions of the invention are administered in combination with an α (C \times C) chemokine selected from the group consisting of gamma-interferon inducible protein-10 (γ IP-10), interleukin-8 (IL-8), platelet factor-4 (PF4), neutrophil activating protein (NAP-2), GRO- α , GRO- β , GRO- γ , neutrophil-activating peptide (ENA-78), granulocyte chemoattractant protein-2 (GCP-2), and stromal cell-derived factor-1 (SDF-1, or pre-B cell stimulatory factor (PBSF)); and/or a β (CC) chemokine selected from the group consisting of: RANTES (regulated on activation, normal T expressed and secreted), macrophage inflammatory protein-1 alpha (MIP-1 α), macrophage inflammatory protein-1 beta (MIP-1 β), monocyte chemoattractant protein-1 (MCP-1), monocyte chemotactic protein-2 (MCP-2), monocyte chemotactic protein-3 (MCP-3), monocyte chemotactic protein-4 (MCP-4), macrophage inflammatory protein-1 gamma (MIP-1 γ), macrophage inflammatory protein-3 alpha (MIP-3 α), macrophage inflammatory protein-3 beta (MIP-3 β), macrophage inflammatory protein-4 (MIP-4/DC-CK-1/PARC), eotaxin, Exodus, and I-309; and/or the γ (C) chemokine, Ilyphotactin.

In another embodiment, the antibody and antibody compositions of the invention are administered with chemokine beta-s, chemokine beta-1, and/or macrophage inflammatory

protein-4. In a preferred embodiment, the antibody and antibody compositions of the invention are administered with chemokine beta-8.

In an additional embodiment, the antibody and antibody compositions of the invention are administered in combination with an IL-4 antagonist. IL-4 antagonists that may be administered with the antibody and antibody compositions of the invention include, but are not limited to: soluble IL-4 receptor polypeptides, multimeric forms of soluble IL-4 receptor polypeptides; anti-IL-4 receptor antibodies that bind the IL-4 receptor without transducing the biological signal elicited by IL-4, anti-IL4 antibodies that block binding of IL-4 to one or more IL-4 receptors, and muteins of IL-4 that bind IL-4 receptors but do not transduce the biological signal elicited by IL-4. Preferably, the antibodies employed according to this method are monoclonal antibodies (including antibody fragments, such as, for example, those described herein).

In an additional embodiment, the antibody and antibody compositions of the invention are administered in combination with fibroblast growth factors. Fibroblast growth factors that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

Demonstration of Therapeutic or Prophylactic Utility of a Composition

The compounds of the invention are preferably tested in vitro, and then in vivo for the desired therapeutic or prophylactic activity, prior to use in humans. For example, in vitro assays which can be used to determine whether administration of a specific antibody or composition of the present invention is indicated, include in vitro cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered an antibody or composition of the present invention, and the effect of such an antibody or composition of the present invention upon the tissue sample is observed. In various specific embodiments, in vitro assays can be carried out with representative cells of cell types involved in a patient's disorder, to determine if an antibody or composition of the present invention has a desired effect upon such cell types. Preferably, the antibodies or compositions of the invention are also tested in in vitro assays and animal model systems prior to administration to humans.

Antibodies or compositions of the present invention for use in therapy can be tested for their toxicity in suitable animal model systems, including but not limited to rats, mice, chicken, cows, monkeys, and rabbits. For in vivo testing of an antibody or composition's toxicity any animal model system known in the art may be used.

Antibodies or compositions of the invention can also be tested for their ability to reduce bacterial numbers in in vitro and in vivo assays known to those of skill in the art. Antibodies or compositions of the invention can also be tested for their ability to alleviate one or more symptoms associated with anthrax disease or anthrax toxin poisoning. Antibodies or antibody compositions of the invention can also be tested for their ability to decrease the time course of the infectious disease. Further, antibodies or compositions of the invention can be tested for their ability to increase the survival period of animals suffering from anthrax or anthrax toxin poisoning. Techniques known to those of skill in the art can be used to analyze the function of the antibodies or compositions of the invention in vivo.

Efficacy in treating or preventing bacterial (e.g. *Bacillus anthracis*) infection may be demonstrated by detecting the ability of an antibody or composition of the invention to inhibit the replication of the bacteria, to inhibit transmission or prevent the bacteria from establishing itself in its host, or to prevent, ameliorate or alleviate the symptoms of disease progression. The treatment is considered therapeutic if there is, for example, a reduction in bacterial load, amelioration of one or more symptoms, or a decrease in mortality and/or morbidity following administration of an antibody or composition of the invention.

Panels/Mixtures

The present invention also provides for mixtures of antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that specifically bind to PA or a fragment or variant thereof, wherein the mixture has at least one, two, three, four, five or more different antibodies of the invention. In specific embodiments, the invention provides mixtures of at least 2, preferably at least 4, at least 6, at least 8, at least 10, at least 12, at least 15, at least 20, or at least 25 different antibodies that specifically bind to PA or fragments or variants thereof, wherein at least 1, at least 2, at least 4, at least 6, or at least 10, antibodies of the mixture is an antibody of the invention. In a specific embodiment, each antibody of the mixture is an antibody of the invention.

The present invention also provides for panels of antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that specifically bind to PA or a fragment or variant thereof, wherein the panel has at least one, two, three, four, five or more different antibodies of the invention. In specific embodiments, the invention provides for panels of antibodies that have different affinities for PA, different specificities for PA, or different dissociation rates. The invention provides panels of at least 10, preferably at least 25, at least 50, at least 75, at least 100, at least 125, at least 150, at least 175, at least 200, at least 250, at least 300, at least 350, at least 400, at least 450, at least 500, at least 550, at least 600, at least 650, at least 700, at least 750, at least 800, at least 850, at least 900, at least 950, or at least 1000, antibodies. Panels of antibodies can be used, for example, in 96 well plates for assays such as ELISAs.

The present invention further provides for compositions comprising, one or more antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants of the invention). In one embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH domains of a one or more of the scFvs referred to in Table 1 or recombinant antibodies expressed by the cell lines referred to in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR1s of a VH domain of one or more of the scFvs referred to in Table 1 or recombinant antibodies expressed by the cell lines referred to in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR2s of a VH domain of one or more of the scFvs referred to in Table 1 or recombinant antibodies expressed by the cell lines referred to

in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR3s as of a VH domain of one or more of the scFvs or recombinant antibodies expressed by the cell lines referred to in Table 1, or a variant thereof.

Other embodiments of the present invention providing for compositions comprising, one or more antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants of the invention) are listed below. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL domains of one or more of the scFvs referred to in Table 1 or recombinant antibodies expressed by the cell lines referred to in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR1s domains of one or more of the scFvs referred to in Table 1 or recombinant antibodies expressed by the cell lines referred to in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR2s of one or more of the scFvs referred to in Table 1 or recombinant antibodies expressed by the cell lines referred to in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR3s domains of one or more of the scFvs referred to in Table 1 or recombinant antibodies expressed by the cell lines referred to in Table 1, or a variant thereof.

Kits

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In an alternative embodiment, a kit comprises an antibody fragment that specifically binds to PA polypeptides or fragments or variants thereof. In a specific embodiment, the kits of the present invention contain a substantially isolated PA polypeptide or fragment or variant thereof as a control. Preferably, the kits of the present invention further comprise a control antibody which does not react with PA polypeptides or fragments or variants thereof. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to PA polypeptides (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate). In specific embodiments, the kit may include a recombinantly

produced or chemically synthesized PA polypeptide. The PA provided in the kit may also be attached to a solid support. In a more specific embodiment the detecting means of the above-described kit includes a solid support to which PA is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to PA can be detected by binding of the said reporter-labeled antibody.

In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with PA polypeptides, and means for detecting the binding of PA polypeptides to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

In specific embodiments, a kit of the invention comprises a means for administering an antibody to an animal, preferably a human. Means for administering an antibody to an animal include a syringe.

Gene Therapy

In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a anthrax or anthrax toxin poisoning, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

For general reviews of the methods of gene therapy, see Goldspiel et al., *Clinical Pharmacy* 12:488-505 (1993); Wu and Wu, *Biotherapy* 3:87-95 (1991); Tolstoshev, *Ann. Rev. Pharmacol. Toxicol.* 32:573-596 (1993); Mulligan, *Science* 260:926-932 (1993); and Morgan and Anderson, *Ann. Rev. Biochem.* 62:191-217 (1993); May, *TIBTECH* 11(5):155-215 (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), *Current Protocols in Molecular Biology*, John Wiley & Sons, NY (1993); and Kriegler, *Gene Transfer and Expression, A Laboratory Manual*, Stockton Press, NY (1990).

In a preferred aspect, a composition of the invention comprises, or alternatively consists of, nucleic acids encoding an antibody, said nucleic acids being part of an expression vector that expresses the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acids have promoters, preferably heterologous promoters, operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, *Proc. Natl. Acad. Sci. USA* 86:8932-8935 (1989); Zijlstra et al., *Nature* 342:435-438 (1989). In specific embodiments, the expressed antibody molecule is an scFv; alterna-

tively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments or variants thereof, of an antibody.

Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid-carrying vectors, or indirect, in which case, cells are first transformed with the nucleic acids in vitro, then transplanted into the patient. These two approaches are known, respectively, as in vivo or ex vivo gene therapy.

In a specific embodiment, the nucleic acid sequences are directly administered in vivo, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, e.g., by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, e.g., by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Pat. No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, e.g., Wu and Wu, *J. Biol. Chem.* 262:4429-4432 (1987)) (which can be used to target cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand-comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted in vivo for cell specific uptake and expression, by targeting a specific receptor (see, e.g., PCT Publications WO 92/06 180; WO 92/22715; WO92/203 16; WO93/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, *Proc. Natl. Acad. Sci. USA* 86:8932-8935 (1989); Zijlstra et al., *Nature* 342:435-438 (1989)).

In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention or fragments or variants thereof are used. For example, a retroviral vector can be used (see Miller et al, *Meth. Enzymol.* 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., *Biotherapy* 6:29 1-302 (1994), which describes the use of a retroviral vector to deliver the *mdr 1* gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., *J. Clin. Invest.* 93:644-651 (1994); Klein et al., *Blood* 83:1467-1473 (1994); Salmons and Gunzberg, *Human Gene Therapy*, 4:129-141 (1993); and Grossman and Wilson, *Curr. Opin. in Genetics and Devel.* 3:110-114 (1993).

Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, *Current*

Opinion in Genetics and Development 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout et al., Human Gene Therapy 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., Science 252:431-434 (1991); Rosenfeld et al., Cell 68:143-155 (1992); Mastrangeli et al., J. Clin. Invest. 91:225-234 (1993); PCT Publication WO94/12649; and Wang, et al., Gene Therapy 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., Proc. Soc. Exp. Biol. Med. 204:289-300 (1993); U.S. Pat. No. 5,436,146).

Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

In this embodiment, the nucleic acid is introduced into a cell prior to administration in vivo of the resulting recombinant cell. Such introduction can be carried out by any method known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, Meth. Enzymol. 217:599-718 (1993); Cohen et al., Meth. Enzymol. 217:718-644 (1993); Clin. Pharma. Ther. 29:69-92m (1985)) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as T lymphocytes, B lymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody or fragment thereof are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered in vivo for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained in vitro can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT

Publication WO 94/08598; Stemple and Anderson, Cell 71:973-985 (1992); Rheinwald, Meth. Cell Bio. 21A:229 (1980); and Pittelkow and Scott, Mayo Clinic Proc. 71:771 (1986)).

In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by controlling the presence or absence of the appropriate inducer of transcription.

EXAMPLES

Example 1

Isolation and Characterization of scFvs Referred to in Table 1

Maxisorp tubes (Nunc) were coated overnight with 10 micrograms/ml of PA83 protein in PBS at 4° C. Unbound PA was removed by washing the tubes with 1×PBST and 1×PBS followed by filling the tubes with a 3% milk solution in 1×PBS for one hour to block any exposed tube surface. Approximately 10¹³ TU of phage from phage display libraries available from Cambridge Antibody Technology (Cambridgeshire, United Kingdom) diluted in 3% milk/1×PBS was applied to the tube and incubated for at least 60 minutes at room temperature. Tubes were washed 10 times with PBS 0.1% Tween-20 and 10 times with PBS. Phage are eluted by adding 1 ml of 100 mM triethylamine with gentle shaking after which the solution is immediately neutralized with 0.5 ml of 1.0M Tris-HCl, pH 7.4. Phage were then used to infect 10 ml of mid-log *E. coli* TG1 by incubating eluted phage with bacteria for 30 minutes at 37° C. The *E. coli* were then plated on 2XYT plates containing 2% glucose and 100 micrograms/ml ampicillin. The resulting bacterial library was then rescued with delta gene 3 helper phage to prepare phage for a subsequent round of selection. This process is usually repeated for a total of 2-4 rounds of affinity purification. Specific enrichment of PA binding phage can be monitored during the selection process. Individual clones from both the second and the third rounds of selections were screened for the ability to bind to PA protein using the assay protocol described below.

PA Binding Assay Protocol for scFv-Phage Library Screening

Purified full-length PA protein (PA83) was labeled with Biotin-LC-Sulfo-NHS (Pierce) at a molar challenge ratio of 8:1 in PBS, 8.0 for 60 minutes at 23° C. Protein was separated from free label using a NAP 5 gel filtration column (Amersham-Pharmacia Biotech) following manufacturer's protocol. A polyclonal antibody specific for the M13 phage coat (Amersham-Pharmacia Biotech) was labeled with the electrochemiluminescent reporter Origen-TAG-NHS ((Origen-TAG), IGEN International, Inc.) at a molar challenge ratio of 5:1 in PBS, 8.0 buffer for 60 minutes at 23° C. Protein was separated from free label using a NAP 5 gel filtration column (Amersham-Pharmacia Biotech) following manufacturer's protocol. The amount of incorporated Origen-TAG label was determined by measuring the absorbance of the undiluted labeling reaction at 455 nm in a 1 cm cuvette and dividing by 13,700 (extinction coefficient of Ori-TAG label) to obtain the Ori-TAG label concentration in moles per liter. This number was divided by the moles per liter IgG concentration in the labeling reaction. Label concentrations used in the assay ranged from 3 to 5 labels per IgG molecule. The biotinylated-

PA83 and Origen-TAG labeled anti-M13 antibody were used to screen phage clones for PA binding as described below.

Individual *E. Coli* colonies containing phagemid were inoculated into 96 well plates containing 100 microliters 2xTY+100 micrograms/ml ampicillin+2% glucose per well. Plates were incubated 37 C for 4 hours, shaking. M13K07 helper phage was added to each well at a multiplicity of infection (MOI) of 2 to 10 and the plates were incubated for a further 1 hour at 37 C. The plates were centrifuged in a benchtop centrifuge at 2000 rpm for 10 minutes. The supernatant was removed and cell pellets were resuspended in 100 microliters 2xTY+100 micrograms/ml ampicillin+50 micrograms/ml kanamycin and incubated at 30 C overnight, with vigorous shaking. The next day, plates were centrifuged at 2000 rpm for 10 min and 100 microliters of phage-containing supernatant from each well carefully transferred into a fresh 96-well plate.

The supernatants containing scFv-phage were screened for binding to PA83 using the following protocol: In a 96 well plate, 5 microliters of scFv-phage were combined with 150 microliters of 0.5 micrograms/ml Biotin-PA83 and 0.5 micrograms/ml Origen-Tag labeled anti-M13 polyclonal antibody and 20 micrograms of Streptavidin coated magnetic beads (DynaM280 beads). The plate was sealed and mixed vigorously for 60 minutes at room temperature. The electrochemiluminescent (ECL) signal was measured in each well of the plate using an Origen M8 series ECL analyzer (IGEN International, Inc). Wells that showed ECL signals that were 5-fold above the assay background were scored as positive PA binders and submitted for sequencing.

The complete nucleotide sequence of the scFv insert from 980 PA positive binding phage clones was determined and a numerical summary of the sequence diversity and ability to bind PA in the above-described PA Binding Assay is presented in the Table 4 below.

TABLE 4

Summary of ScFv Groups and CDR 3 Sequences for PA-Binding Phage Clones

Group	HC group, LC group	Representative scFv clone	HC CDR 3 Seq.	SEQ ID NO:	LC CDR 3 Seq.	SEQ ID NO:	PA Binding Pos/Neg
1	HC group 115, LC group 122:	PWB2001	HSPGDYAFDY	66	ASWDDSLNGRV	299	+
2	HC group 115, LC group 135:	PWB2855	HSPGDYAFDY	67	ASWDDSLKSRV	300	+
3	HC group 115, LC group 137:	PWB2916	HSPGDYAFDY	68	ASWDDSVNGRV	301	+
4	HC group 116, LC group 123:	PWB2002	AGRRTQLQPR DFLFEY	69	NSRDSSGNHVV	302	+
5	HC group 116, LC group 127:	PWB2175	AGRRTQLQPR DFLFEY	70	NSRDSSGNHVV	303	+
6	HC group 116, LC group 131:	PWB2362	AGRRTQLQPR DFLFEY	71	NSRDSSGNHVV	304	+
7	HC group 116, LC group 132:	PWB2447	AGRRTQLQPR DFLFEY	72	NSRDSSGNHVV	305	+
8	HC group 116, LC group 134:	PWB2754	AGRRTQLQPR DFLFEY	73	NSRDSSGNHVV	306	+
9	HC group 117, LC group 122:	PWB2006	HSPGDYAFDY	74	ASWDDSLNGRV	307	+
10	HC group 118, LC group 124:	PWB2008	HSPGDYAFDY	75	ASWDDSLNGRV	308	+
11	HC group 119, LC group 123:	PWB2016	ASYLSTSSSLDY	76	NSRDSSGNHVV	309	+
12	HC group 119, LC group 133:	PWB2562	ASYLSTSSSLDY	77	NSRDSSGNHVV	310	+
13	HC group 120, LC group 123:	PWB2018	AGRRTQLQPR DFLFEY	78	NSRDSSGNHVV	311	+
14	HC group 121, LC group 125	PWB2043	DLDSSSTIPHRE YGMDV	79	HSRDSSGNHVL	312	+
15	HC group 122, LC group 123:	PWB2061	AGRRTQLQPR DFLFEY	80	NSRDSSGNHVV	313	+
16	HC group 123, LC group 123:	PWB2144	AGRRTQLQPR DFLFEY	81	NSRDSSGNHVV	314	+
17	HC group 124, LC group 126:	PWB2153	AGRRTQLQPR DFLFEY	82	NSRDSSGNHVV	315	+
18	HC group 125, LC group 123:	PWB2202	ASNLTSSSLDY	83	NSRDSSGNHVV	316	+
19	HC group 126, LC group 128:	PWB2216	SGSSWSHFDF	84	SSYTTRSTRV	317	+
20	HC group 127, LC group 129:	PWB2281	GSPTGDLNVDFDY	85	NSRDSSGNHVV	318	+
21	HC group 128, LC group 130:	PWB2301	HSPGDYAFDY	86	ASWDDSLNGRV	319	+
22	HC group 129, LC group 122:	PWB2323	VRDIRPGDYAFDY	87	ASWDDSLNGRV	320	+
23	HC group 130, LC group 123:	PWB2325	AGRRTQLQPR DFLFEY	88	NSRDSSGNHVV	321	+
24	HC group 131, LC group 123:	PWB2334	Not Determined		NSRDSSGNHVV	322	+
25	HC group 132, LC group 122:	PWB2341	HSPGDYAFDY	89	ASWDDSLNGRV	323	+

TABLE 4-continued

Summary of ScFv Groups and CDR 3 Sequences for PA-Binding Phage Clones							
Group	HC group, LC group	Representative scFv clone	HC CDR 3 Seq.	SEQ ID NO:	LC CDR 3 Seq.	SEQ ID NO:	PA Binding Pos/Neg
26	HC group 133, LC group 123:	PWB2353	ASYLSTSPSLDY	90	NSRDSSGNHVV	324	+
27	HC group 134, LC group 123:	PWB2363	AGRRTQLQPR DFLFY	91	NSRDSSGNHVV	325	+
28	HC group 135, LC group 122:	PWB2364	HSPGDYAFDY	92	ASWDDSLNGRV	326	+
29	HC group 136, LC group 123:	PWB2376	AGRRTQLQPR DFLFY	93	NSRDSSGNHVV	327	+
30	HC group 137, LC group 128:	PWB2435	SGSSWSHFDF	94	SSYTTRSTRV	328	+
31	HC group 138, LC group 123:	PWB2456	AGRRTQLPPR DFLFY	95	NSRDSSGNHVV	329	+
32	HC group 139, LC group 122:	PWB2466	HSPGDYAFDY	96	ASWDDSLNGRV	330	+
33	HC group 140, LC group 123:	PWB2502	ASNLTSPSLDY	97	NSRDSSGNHVV	331	+
34	HC group 141, LC group 123:	PWB2532	AGRRTQLQPI DFLFY	98	NSRDSSGNHVV	332	+
35	HC group 142, LC group 123:	PWB2617	AGRRTQLQPR DFLFY	99	NSRDSSGNHVV	333	+
36	HC group 143, LC group 122:	PWB2756	HSPGDYAFDY	100	ASWDDSLNGRV	334	+
37	HC group 144, LC group 123:	PWB2849	AGRRTQLQPR DFLFY	101	NSRDSSGNHVV	335	+
38	HC group 145, LC group 136:	PWB2873	SGSGYSGYDFP YYYGMDV	102	HSRDSSGNHVL	336	+
39	HC group 146, LC group 123:	PWB2878	AGRRTQLQPR DFLFY	103	NSRDSSGNHVV	337	+
40	HC group 147, LC group 123:	PWB2955	Not Determined		NSRDSSGNHVV	338	+
41	HC group 2, LC group 2:	PWC2008	AGRRTQLQPR DFLFY	104	NSRDSSGNHVV	339	+
42	HC group 2, LC group 163:	PWC2065	AGRRTQLQPR DFLFY	105	NSRDSSGNHVV	340	+
43	HC group 2, LC group 188:	PWC2963	AGRRTQLQPR DFLFY	106	NSRDSSGNHVV	341	+
44	HC group 140, LC group 155:	PWC2002	DSSSGWFFIDY	107	QSYDSSLGGYVI	342	+
45	HC group 140, LC group 160:	PWC2043	ARDSSSGWFFIDY	108	QSYDSSLGGYVI	343	+
46	HC group 140, LC group 165:	PWC2302	DSSSGWFFIDY	109	QSYDSSLGGYVI	344	+
47	HC group 140, LC group 166:	PWC2308	DSSSGWFFIDY	110	QSYDSSLGGYVI	345	+
48	HC group 140, LC group 167:	PWC2310	DSSSGWFFIDY	111	QSYDSSLGGYVI	346	+
49	HC group 140, LC group 169:	PWC2361	DSSSGWFFIDY	112	QSYDSSLGGYVI	347	+
50	HC group 140, LC group 172:	PWC2461	DSSSGWFFIDY	113	QSYDSSLGGYVI	348	+
51	HC group 140, LC group 175:	PWC2616	DSSSGWFFIDY	114	QSYDSSLGGYVI	349	+
52	HC group 140, LC group 176:	PWC2632	DSSSGWFFIDY	115			+
53	HC group 140, LC group 179:	PWC2678	DSSSGWFFIDY	116	QSYDSSLGGYVI	350	+
54	HC group 140, LC group 183:	PWC2748	DSSSGWFFIDY	117	QSYDSSLGGYGI	351	+
55	HC group 141, LC group 156:	PWC2004	SRYSSSPFRGGLDV	118	HSYDSSISGGI	352	+
56	HC group 141, LC group 157:	PWC2007	SRYSSSPFRGGLDV	119	HSYDSSISGWI	353	+
57	HC group 141, LC group 158:	PWC2010	SRYSSSPFRGGLDV	120	HSYDSSISGWI	354	+
58	HC group 141, LC group 159:	PWC2021	SRYSSSPFRGGLDV	121	HSYDSSIRGWI	355	+
59	HC group 141, LC group 161:	PWC2046	SRYSSSPFRGGLDV	122	HSYDSSIRGGI	356	+
60	HC group 141, LC group 162:	PWC2057	SRYSSSPFRGGLDV	123	HSYDSSISGGI	357	+
61	HC group 141, LC group 164:	PWC2093	SRYSSSPFRGGLDV	124	HSYDSSISAWI	358	+
62	HC group 141, LC group 170:	PWC2375	SRYSSSPFRGGLDV	125	HSYDSSISGWI	359	+

TABLE 4-continued

Summary of ScFv Groups and CDR 3 Sequences for PA-Binding Phage Clones							
Group	HC group, LC group	Representative scFv clone	HC CDR 3 Seq.	SEQ ID NO:	LC CDR 3 Seq.	SEQ ID NO:	PA Binding Pos/Neg
63	HC group 141, LC group 178:	PWC2652	SRYSSSPFRGGLDV	126	HSYDSSISGWI	360	+
64	HC group 141, LC group 187:	PWC2939	SRYSSSPFRGGLDV	127	HSYDSSISGWI	361	+
65	HC group 142, LC group 160:	PWC2068	SSSGCLFIDY	128	QSYDSSLGGYVI	362	+
66	HC group 143, LC group 157:	PWC2131	SRYSSSPFRGGLDV	129	HSYDSSISGWI	363	+
67	HC group 143, LC group 158:	PWC2892	SRYSSSPFRGGLDV	130	HSYDSSISGWI	364	++
68	HC group 144, LC group 155:	PWC2151	DSSSGWFFIDY	131	QSYDSSLGGYVI	365	+
69	HC group 145, LC group 157:	PWC2156	SRYSSSPFRGGLDV	132	HSYDSSISGWI	366	+
70	HC group 146, LC group 157:	PWC2321	SRYSSSPFRGGLDV	133	HSYDSSISGWI	367	+
71	HC group 147, LC group 157:	PWC2332	SRYSSSPFRGGLDV	134	HSYDSSISGWI	368	+
72	HC group 148, LC group 168:	PWC2350	DSSSGWFFI	135	QSYDSSLGGYVI	369	+
73	HC group 149, LC group 155:	PWC2386	SSSGWLFIDY	136	QSYDSSLGGYVI	370	+
74	HC group 150, LC group 171:	PWC2393	SRYSSSPFRGGLDV	137	HSYDSSISGWI	371	+
75	HC group 151, LC group 157:	PWC2412	SRYSSSPFRGGLDV	138	HSYDSSISGWI	372	+
76	HC group 152, LC group 155:	PWC2424	DSSSGWFFIDY	139	QSYDSSLGGYVI	373	+
77	HC group 153, LC group 155:	PWC2431	DSSSGWFFIDY	140	QSYDSSLGGYVI	374	+
78	HC group 154, LC group 157:	PWC2436	SRYSSSPFRGGLDV	141	HSYDSSISGWI	375	+
79	HC group 155, LC group 155:	PWC2444	DSSSGWFFIDY	142	QSYDSSLGGYVI	376	+
80	HC group 156, LC group 173:	PWC2590	TYPYGGGTAFDY	143	QSYDSELSGSEL	377	-
81	HC group 157, LC group 174:	PWC2606	NAFDY	144	NSLDSRGQRVI	378	+
82	HC group 158, LC group 177:	PWC2643	SAKSGWKSTFDV	145	ALYLGGGLSWV	379	-
83	HC group 159, LC group 180:	PWC2682	No seq.		AAWDDSLSAYV	380	-
84	HC group 160, LC group 181:	PWC2691	DSSSGWLFIDY	146	QSYDSSLGGYVI	381	+
85	HC group 161, LC group 157:	PWC2710	SRYSSSPFRGGLDV	147	HSYDSSISGWI	382	+
86	HC group 161, LC group 182:	PWC2722	SRYSSSPFRGGLDV	148	HSYDSSISGWI	383	+
87	HC group 162, LC group 184:	PWC2758	DSSSGWLFIDY	149	QSYDSSLGGYVI	384	+
88	HC group 163, LC group 185:	PWC2771	DSSSGWLFIDY	150	QSYDSSLGGYVI	385	+
89	HC group 164, LC group 157:	PWC2792	SRYSSSPFRGGLDV	151	HSYDSSISGWI	386	+
90	HC group 165, LC group 186:	PWC2901	QMIMAARC	152	QSFNRLRGFVV	387	-
91	HC group 166, LC group 155:	PWC2972	DSSSGWFFI	153	QSYDSSLGGYVI	388	+
92	HC group 167, LC group 155:	PWC2980	DSSSGWFFI	154	QSYDSSLGGYVI	389	+
93	HC group 148, LC group 138	PWD0103	VDHKWDLFPDY	155	ATWDDNLNGWV	390	+
94	HC group 148, LC group 194:	PWD0332	VDHKWDLFPDY	156	ATWDDSLNGWV	391	+
95	HC group 148, LC group 249:	PWD0853	VDHKWDLFPDY	157	ATWDDSLNGWV	392	+
96	HC group 148, LC group 272:	PWD1070	VDHKWDLFPDY	158	AAWDDSLNGWV	393	+
97	HC group 149, LC group 139:	PWD0104	LLRGGSTYLD AFDN	159	QVWDRSNGHV	394	+
98	HC group 149, LC group 199:	PWD0384	LLRGGSTYLD AFDN	160	QVWDRSNGHV	395	+
99	HC group 150, LC group 140:	PWD0106	GWGVFDI	161	AAWDDSLDGWV	396	+

TABLE 4-continued

Summary of ScFv Groups and CDR 3 Sequences for PA-Binding Phage Clones							PA Binding Pos/Neg
Group	HC group, LC group	Representative scFv clone	HC CDR 3 Seq.	SEQ ID NO:	LC CDR 3 Seq.	SEQ ID NO:	
100	HC group 151, LC group 141:	PWD0108	VDHNWDLFPDY	162	SAWDDSLNGWV	397	+
101	HC group 151, LC group 143:	PWD0111	VDHNWDLFPDY	163	ASWDDDLNGWV	398	+
102	HC group 151, LC group 195:	PWD0336	VDHNWDLFPDY	164	AVWDDRMNGWE	399	+
103	HC group 151, LC group 208:	PWD0435	VDHNWDLFPDY	165	AAWDDSLNGWV	400	+
104	HC group 151, LC group 234:	PWD0757	VDHNWDLFPDY	166	AVWDDRLNGWE	401	+
105	HC group 151, LC group 248:	PWD0848	VDHNWDLFPDY	167	VDHNWDLFPD	402	+
106	HC group 151, LC group 253:	PWD0875	VDHNWDLFPDY	168	AAWDDSLSGWM	403	+
107	HC group 151, LC group 257:	PWD0925	VDHNWDLFPDY	169	ASWDDDLKSWV	404	+
108	HC group 151, LC group 269:	PWD1048	VDHNWDLFPDY	170	AAWDDSLSGWV	405	+
109	HC group 152, LC group 142:	PWD0109	VDHNWDLFPDY	171	ATWDDSLKGWV	406	+
110	HC group 152, LC group 164:	PWD0171	VDHNWDLFPDY	172	QSKSIPIT	407	-
111	HC group 152, LC group 197:	PWD0366	VDHNWDLFPDY	173	VAWDDSLNGWM	408	+
112	HC group 152, LC group 214:	PWD0470	VDHNWDLFPDY	174	AAWDDSLSGWV	409	+
113	HC group 153, LC group 144:	PWD0112	VDHKWDLFPDY	175	AAWDDSLKGWV	410	+
114	HC group 153, LC group 227:	PWD0679	VDHKWDLFPDY	176	SAWDDGLSGWV	411	+
115	HC group 154, LC group 145:	PWD0114	VDHKWDLFPDY	177	ATWDDSLPLV	412	+
116	HC group 154, LC group 215:	PWD0526	VDHKWDLFPDY	178	EAWDDSLSGPA	413	+
117	HC group 154, LC group 239:	PWD0810	VDHKWDLFPDY	179	AAWDDNLSP	414	-
118	HC group 154, LC group 267:	PWD1012	VDHKWDLFPDY	180	QTYRTPIT	415	+
119	HC group 154, LC group 270:	PWD1050	VDHKWDLFPDY	181	GTWDSRLYVGQV	416	+
120	HC group 155, LC group 146:	PWD0118	VDHNWDLFPDY	182	AAWDDSLNGWV	417	+
121	HC group 155, LC group 172:	PWD0205	VDHNWDLFPDY	183	AAWDDSLNGWV	418	+
122	HC group 155, LC group 241:	PWD0813	VDHNWDLFPDY	184	ATWDDSLNHVV	419	+
123	HC group 155, LC group 244:	PWD0827	VDHNWDLFPDY	185	AAWDDSLNGHWV	420	+
124	HC group 155, LC group 271:	PWD1063	VDHNWDLFPDY	186	AAWDDSLSGVL	421	+
125	HC group 156, LC group 147:	PWD0121	YVADTSKDVFDI	187	NSRDSSGNVV	422	+
126	HC group 157, LC group 148:	PWD0123	VASTALYFDN	188	ASWDDTLKGGV	423	+
127	HC group 158, LC group 149:	PWD0124	GVYNWNSAAKFDY	189	QSYDNSLSGSE	424	+
128	HC group 159, LC group 150:	PWD0127	TYYYVYYNYMDV	190	NSRDSSGDPVT	425	+
129	HC group 160, LC group 151:	PWD0130	VAHGWHLSPDY	191	SAWDDSLKGWV	426	+
130	HC group 161, LC group 152:	PWD0133	SLFRVRGVFFDY	192	ASRDSSANQHWV	427	+
131	HC group 161, LC group 158:	PWD0150	SLFRVRGVFFDY	193	QSYDSSTGI	428	+
132	HC group 162, LC group 153:	PWD0135	GPAGLQLSLDI	194	AAWDDSLNGLV	429	+
133	HC group 163, LC group 154:	PWD0136	VDHRWDLFPDY	195	STWDGSLNGWV	430	+
134	HC group 164, LC group 155:	PWD0139	VDHKWDLFPDY	196	AAWDDSLNGWV	431	+
135	HC group 164, LC group 163:	PWD0169	VDHKWDLFPDY	197	STWDDSLRGVV	432	+
136	HC group 164, LC group 181:	PWD0254	VDHKWDLFPDY	198	AVWDDSLNGWV	433	+

TABLE 4-continued

Summary of ScFv Groups and CDR 3 Sequences for PA-Binding Phage Clones							
Group	HC group, LC group	Representative scFv clone	HC CDR 3 Seq.	SEQ ID NO:	LC CDR 3 Seq.	SEQ ID NO:	PA Binding Pos/Neg
137	HC group 164, LC group 240:	PWD0811	VDHKWDLFPDY	199	APWDDSLNGWV	434	+
138	HC group 165, LC group 156:	PWD0146	ARDYYFGMDV	200	SAWDDSLHGPV	435	+
139	HC group 166, LC group 157:	PWD0147	GPAGLQLSLDI	201	AAWDDSLNGVV	436	+
140	HC group 167, LC group 159:	PWD0151	DRSKLNAGYFDS	202	QSYDNSLSAW	437	+
141	HC group 168, LC group 160:	PWD0154	TKYSSIVFDL	203	AAWDDSLNVVV	438	+
142	HC group 169, LC group 161:	PWD0157	FRFLVWYGEAYFDY	204	SSRDNSGDRVLV	439	+
143	HC group 170, LC group 162:	PWD0164	VRGQLLAFDI	205	AAWDDSLNGWV	440	+
144	HC group 171, LC group 165:	PWD0175	VDHKWDLFPDY	206	ATWDDSLRGWV	441	+
145	HC group 171, LC group 182:	PWD0258	VDHKWDLFPDY	207	ATWDDSVRGWV	442	+
146	HC group 172, LC group 166:	PWD0176	GPAGLQLSLDI	208	ATWDDSLSGWV	443	+/-
147	HC group 173, LC group 167:	PWD0177	TKYSSIVFDL	209	AAWDDSLNAVL	444	+
148	HC group 174, LC group 168:	PWD0183	AVWDDSLNGH	210	VDRRWDLFPDY	445	+
149	HC group 175, LC group 169:	PWD0187	TKYSSIVFDL	211	ASWDDSLNGV	446	+
150	HC group 176, LC group 170:	PWD0189	LDHKWDLFPDY	212	EAWDDSLSGPA	447	+/-
151	HC group 177, LC group 171:	PWD0190	VDHNWDLFPDY	213	GTWDSRLSAVV	448	+
152	HC group 178, LC group 173:	PWD0211	EYYRWGYSYAN	214	NSRDSSGNPVV	449	+/-
153	HC group 179, LC group 174:	PWD0218	VDHKWDLFPDY	215	TAWDDSLNGWV	450	+
154	HC group 180, LC group 175:	PWD0228	VDHNWDLFPDY	216	AAWDDILNGWV	451	+
155	HC group 181, LC group 176:	PWD0229	SLFRVRGVFFDY	217	NSRDSSGNHVV	452	+
156	HC group 181, LC group 193:	PWD0329	SLFRVRGVFFDY	218	QAWDSSTTWE	453	+
157	HC group 181, LC group 233:	PWD0754	SLFRVRGVFFDY	219	ETWDTLSVLV	454	+
158	HC group 182, LC group 177:	PWD0233	DLGVGRYFDY	220	SSRDNSGDPL	455	+
159	HC group 182, LC group 223:	PWD0611	DLGVGRYFDY	221	SSRDNSGDPL	456	+
160	HC group 183, LC group 178:	PWD0243	SLFRVRGVFFDY	222	NSRDSSGNHVV	457	+
161	HC group 184, LC group 179:	PWD0246	DRSKLNAGYFDS	223	QSYDSSLAYV	458	+
162	HC group 184, LC group 263:	PWD0968	DRSKLNAGYFDS	224	QSYDSGLSAVV	459	+
163	HC group 185, LC group 180:	PWD0248	LDHNWDLFPDY	225	ASWDDSLSGWV	460	+
164	HC group 185, LC group 207:	PWD0427	LDHNWDLFPDY	226	ATWDDSLSGLL	461	+
165	HC group 185, LC group 235:	PWD0766	LDHNWDLFPDY	227	ASWDDSLKGVV	462	+
166	HC group 186, LC group 183:	PWD0259	TKYSSIVFDL	228	AAWDDRLSGPV	463	+
167	HC group 186, LC group 210:	PWD0441	TKYSSIVFDL	229	AAWDDSLNGML	464	+
168	HC group 186, LC group 243:	PWD0824	TKYSSIVFDL	230	AAWDDSLNGP	465	+/-
169	HC group 187, LC group 184:	PWD0268	LDHNWNLFPD	231	ATWDDRLKGFV	466	+
170	HC group 188, LC group 185:	PWD0283	VGGAIRFDS	232	SAWDDSLSGVV	467	+
171	HC group 189, LC group 186:	PWD0288	SVGRSLAFDI	233	AAWDDSLNGHV	468	+
172	HC group 190, LC group 187:	PWD0291	RTGDSCYTSCY	234	QTWDSTTAS	469	+
173	HC group 191, LC group 188:	PWD0294	GPAGLQLSLDI	235	SAWDDSLNGPA	470	+

TABLE 4-continued

Summary of ScFv Groups and CDR 3 Sequences for PA-Binding Phage Clones							
Group	HC group, LC group	Representative scFv clone	HC CDR 3 Seq.	SEQ ID NO:	LC CDR 3 Seq.	SEQ ID NO:	PA Binding Pos/Neg
174	HC group 191, LC group 209:	PWD0440	GPAGLQLSLDI	236	SAWDDSLNGPA	471	+
175	HC group 192, LC group 189:	PWD0305	VDHKWDLFPDY	237	ATWDDTLISGLV	472	+
176	HC group 193, LC group 190:	PWD0308	FTGWYGAFDI	238	ATWDDSVNGPA	473	+
177	HC group 194, LC group 191:	PWD0318	DRYNMVGVLRPDS	239	SSYARSNNFGV	474	-
178	HC group 195, LC group 192:	PWD0323	QIWGRFEY	240	AAWDDRLNGYV	475	+
179	HC group 195, LC group 219:	PWD0587	QIWGRFEY	241	AAWDDSLNGVV	476	+
180	HC group 196, LC group 196:	PWD0339	GYDFWSGFDY	242	QVWDSTSDHRI	477	+
181	HC group 197, LC group 140:	PWD0355	GWGVFDM	243	AAWDDSLDGVV	478	+
182	HC group 198, LC group 198:	PWD0369	VDHKWDLPFDF	244	ASWDDSLDGVV	479	+/-
183	HC group 199, LC group 200:	PWD0389	ARALFRVSGPY	245	SSYSGDVNFIV	480	+
184	HC group 200, LC group 201:	PWD0391	DHPYNWNYFDY	246	QQLNRYPSL	481	-
185	HC group 201, LC group 202:	PWD0392	GAPAVRHGFDY	247	QQYYSTPPT	482	-
186	HC group 202, LC group 203:	PWD0412	VDHKWDLFPDY	248	ATWDDSLKGFV	483	+
187	HC group 203, LC group 204:	PWD0416	FGTGSSLEV	249	AAWDDSLNGVV	484	+
188	HC group 204, LC group 205:	PWD0422	QAFARFEF	250	SSWDDSLNGVV	485	+
189	HC group 205, LC group 206:	PWD0424	NLQDIVATILPFDY	251	GTWDDSLNTYV	486	-
190	HC group 206, LC group 141:	PWD0436	VDHNWDLFPDY	252	SAWDDSLNGWV	487	+
191	HC group 207, LC group 211:	PWD0451	GDPEELRSDS YFYYGMDV	253	QSYDSSLGSGWV	488	-
192	HC group 208, LC group 212:	PWD0454	LDHKWDLPFDDH	254	EAWDDSLSGPA	489	+
193	HC group 209, LC group 213:	PWD0469	TKYSSVAFDL	255	ATWDDSLNGVV	490	+
194	HC group 210, LC group 139:	PWD0525	LLRGGSTYLDADF	256	QVWDRSNGHV	491	+
195	HC group 211, LC group 216:	PWD0541	Not Determined		QQFKSYPLT	492	-
196	HC group 212, LC group 217:	PWD0542	GVYGGGSAGLYFDV	257	QVWDNSSGWV	493	+
197	HC group 213, LC group 218:	PWD0568	GEMATIRY	258	ATWDDSLNGWV	494	+
198	HC group 214, LC group 220:	PWD0588	VDHKWDLFPDY	259	AAWDASLTSWV	495	+
199	HC group 215, LC group 221:	PWD0593	VDHNWDLFPDY	260	AAWDDSLNGVV	496	+
200	HC group 216, LC group 222:	PWD0605	ASSWYLVFDI	261	AAWDDSLNGWV	497	+
201	HC group 216, LC group 259:	PWD0929	ASSWYLVFDI	262	AAWDDSLNGWV	498	+
202	HC group 217, LC group 224:	PWD0615	SLFRVRGVFFDY	263	GTWDDSLSDGKVV	499	+
203	HC group 218, LC group 146:	PWD0635	VDHNWDLFPDY	264	AAWDDSLNGWV	500	+
204	HC group 219, LC group 225:	PWD0638	VDHNWDLFPDY	265	ATWDDSRGGWV	501	+
205	HC group 220, LC group 226:	PWD0648	VDRRWDLFPDY	266	ASWDDSVGSGWV	502	+
206	HC group 221, LC group 228:	PWD0706	VDHKWDLPFDF	267	AAWDDSLNGWV	503	+
207	HC group 222, LC group 229:	PWD0709	GGPFGSSYDV	268	ASWDDSLSGLV	504	+
208	HC group 223, LC group 230:	PWD0718	PTYGPGSFLDH	269	ATWDDSLNGPV	505	+
209	HC group 224, LC group 231:	PWD0721	TRGYSLYFDS	270	ATWDDSLMVG	506	+
210	HC group 225, LC group 232:	PWD0730	VDHNWDLFPDY	271	ATWDDSLNGWV	507	+

TABLE 4-continued

Summary of ScFv Groups and CDR 3 Sequences for PA-Binding Phage Clones							
Group	HC group, LC group	Representative scFv clone	HC CDR 3 Seq.	SEQ ID NO:	LC CDR 3 Seq.	SEQ ID NO:	PA Binding Pos/Neg
211	HC group 226, LC group 236:	PWD0773	GPAGLQLSLDI	272	AVWDDSLNGVI	508	+
212	HC group 227, LC group 237:	PWD0776	GPAGLQLSLDI	273	AAWDDNLNGVV	509	+/-
213	HC group 228, LC group 144:	PWD0791	VDHKWDLPPDY	274	AAWDDSLKGWV	510	+
214	HC group 229, LC group 238:	PWD0808	AGGSSSLVFD	275	AVWDDGLSGWV	511	+
215	HC group 230, LC group 242:	PWD0821	DGSPSNYMDV	276	QQYYSTPIT	512	-
216	HC group 231, LC group 245:	PWD0830	VDHNWDLPPDY	277	VAWDDSLNGWV	513	+
217	HC group 232, LC group 246:	PWD0834	DGDYSSSSLDY	278	QSHDNTLGEV	514	-
218	HC group 233, LC group 247:	PWD0838	VRVPRDGMVDV	279	ASWDDSLTWV	515	+/-
219	HC group 234, LC group 250:	PWD0858	GSYSYIAFDI	280	AAWDDSLSGPVV	516	+
220	HC group 235, LC group 251:	PWD0864	TTVTESDWFDL	281	NSRDSSGNHFDVV	517	+/-
221	HC group 236, LC group 252:	PWD0871	VDHNWDLPPDY	282	ATWDDSLNGFV	518	+
222	HC group 237, LC group 217:	PWD0876	GVYGGGSAGLYFDV	283	QVWDNSSGWV	519	+
223	HC group 238, LC group 254:	PWD0880	GPSGLLLGLDV	284	AVWDDSLNGVL	520	+
224	HC group 239, LC group 255:	PWD0884	VASTALYFDN	285	AAWDDSLTGWV	521	+
225	HC group 240, LC group 256:	PWD0914	LSGVTLHMDV	286	AAWDDSLKGPV	522	+
226	HC group 241, LC group 258:	PWD0928	VRGGNLAFFD	287	AAWDDSLSGWV	523	+
227	HC group 242, LC group 260:	PWD0934	SLFRVRGVFFDY	288	VTWDGSLGVVM	524	+
228	HC group 243, LC group 144:	PWD0948	EDHKWDLPPDY	289	AAWDDSLKGWV	525	+
229	HC group 244, LC group 261:	PWD0949	GALSSFD	290	AAWDDSLNGWV	526	+
230	HC group 245, LC group 262:	PWD0953	QIWGRFEY	291	AAWDDSLNGVV	527	+
231	HC group 246, LC group 146:	PWD0963	ADHNWDLPPDY	292	AAWDDSLNGWV	528	+
232	HC group 247, LC group 264:	PWD0991	AHWGSRVDY	293	AAWDDSLNGVV	529	+
233	HC group 248, LC group 265:	PWD0995	LLRGGSTYLDADFND	294	QVWDRSNGHV	530	+
234	HC group 249, LC group 266:	PWD1003	Not Determined		NSRDSSGNLWV	531	-
235	HC group 250, LC group 268:	PWD1038	EVGSYFDY	295	AAWDDSLNGVV	532	+
236	HC group 251, LC group 273:	PWD1072	VDHNWDLPPDY	296	AAWDDSLNGWV	533	+
237	HC group 252, LC group 274:	PWD1077	SLFRVRGVFFDY	297	NSRDNSGNLWV	534	+
238	HC group 253, LC group 275:	PWD1079	GPRFWTGYDY	298	QQSLTAWV	535	+

Example 2

Affinity Ranking of mAbs to PA and PA Cleavage Site Peptide ELISA

Theoretical considerations suggest that under ideal circumstances antibody concentration at half-maximal antigen binding (EC50) is a measure of affinity. In practical terms it can be used to rank the affinities of antibodies to quickly identify best binders. The lower the antibody concentration required for 50% of plateau binding, the higher is the affinity of the antibody for antigen. In the approach described below, a conventional ELISA is used to generate binding isotherms

for PA antibodies in order to derive their EC-50 values. Additionally, antibodies may be tested for their ability to bind peptides that span the RKKR (residues 193-196 of SEQ ID NO:2) cleavage site in PA.

EC-50 ELISA

Direct Plate Coating with PA: 50 microliters of PA solution (0.2 µg/ml in PBS) is dispensed to individual wells of 96-well plates (Immulon-2, Dynex) sealed with Plate sealers (Advanced Genetic cat. #48461) and incubated overnight at 4° C. Next day the coating solution is removed, plates are washed 4 times with PBS with 0.1% Tween-20 and blocked by incubation with 200 microliters of blocking buffer (PBS, 3% BSA) for 1 hr at room temperature.

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Serial dilutions of anti-PA antibodies are prepared in diluent buffer (PBS, 0.1% Tween-20, 0.1% BSA). Human IgG2 (Sigma, cat #1-4139) is used as a negative control. Two 50 microliter aliquots of each dilution are dispensed into individual wells of coated and blocked plates. The plates are sealed and incubated for 2 hours at room temperature.

Next, plates are washed 4 times with PBST (PBS, 0.1% Tween-20) and 50 microliters of HRP labeled anti-human IgG (Vector, cat #PI-3000) at concentration 1 microgram/milliliter in diluent buffer is dispensed to individual wells. Plates are sealed and incubated for 1 hr at room temperature. In the meantime substrate solution is prepared by dissolving 1 tablet of TMB (Sigma cat #T3405) in 5 ml of water. After the tablet is dissolved, 5 ml of the substrate buffer (0.1 M Na₂PO₄, 0.05 M Citric acid) and 2 microliters of 30% H₂O₂ is added.

Plates are washed 4 times with PBST and 100 microliters of substrate is added to each well. Plates are incubated for 10 min at room temperature and the Absorption at 450 nm is measured on SpectraMax 3000 (Molecular Devices).

Data analysis Data is analyzed using SofMaxPro 3.0. Binding curves (on OD 450 versus concentration graphs) are generated using the four parameter fit model. EC-50 values are calculated automatically as the concentration of the antibody that provides 50% of the maximum binding (maximum binding is characterized by parameter D in the four parameter fit equation).

Cleavage Site Peptide ELISA:

Indirect coating of biotinylated peptides to streptavidin coated plates: One hundred microliters of Streptavidin (Sigma S-4762) solution (1 mg/ml in PBS) is dispensed into individual wells of 96-well plates (Immulon-4, Dynex) sealed with Plate sealers (Advanced Genetic Cat. #48461) and incubated overnight at 4° C. The next day the coating solution is removed, plates are washed 4 times with PBS+0.1% Tween-20 and blocked by incubation with 200 ml of blocking buffer (PBS, 3% BSA) for 1 hour at room temperature.

After blocking, the blocking solution is removed, plates are washed 4 times with PBS+0.1% Tween-20 and 100 microliters per well of biotinylated peptides (1 mg/ml diluted in 0.1% BSA in PBS) is incubated for 1 hour at room temperature. The biotinylated peptides are: sp-186: biotin-SNSRKKRST-SAGPTVPDRDN (amino acids 190-206 of SEQ ID NO:2); sp-187: biotin-QLPELKQKSSNSRKKRSTSAG (amino acids 181-201 of SEQ ID NO:2); and sp-189: biotin-QLPELKQKSSNSRKK (amino acids 181-195 of SEQ ID NO:2). The plates are then washed 4 times with PBST.

100 microliters of 3 dilutions (10 micrograms/ml, 1.0 micrograms/ml and 0.1 micrograms/ml) of purified antibody in duplicate are dispensed into the 96-well plate. The plates are sealed and incubated for 2 hours at room temperature. Plates are washed 4 times with PBST and 100 microliters of HRP-labeled goat anti human IgG (H+ L) (Vector, Cat# PI-3000) are dispensed into individual wells (1 mg/ml in 0.1% BSA in PBST). Plates are sealed and incubated for 1 hour at room temperature. In the meantime, substrate solution is prepared by dissolving 1 tablet of TMB (Sigma, Cat# T3405) in 5 ml of water. After the tablet is dissolved, 5 ml of the substrate buffer (0.1 M Na₂PO₄, 0.05 M Citric acid) and 2 ml of 30% H₂O₂ are added. Plates are washed 4 times with PBST and 100 microliters of substrate is added to each well.

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Plates are incubated for 15 minutes at room temperature and the absorption (at 450 nm) is measured on SpectraMaxPlus (Molecular Devices).

Example 3

Inhibition of Biotinylated PA Binding to Anthrax Receptors

The following protocol may be used to test whether an antibody is able to inhibit the binding of biotinylated PA protein to the anthrax receptor protein (SEQ ID NO:3).

Preparation of ATR Protein

ATR protein was produced by cloning the first 227 amino acid residues of the ATR protein gene (SEQ ID NO:3, Bradley et al, (2001) *Nature* 414:225-229) linked to a polynucleotide encoding the FLAG® tag (Stratagene, La Jolla, Calif.) (amino acid residues DYKDDDDK, SEQ ID NO:43) into a mammalian expression vector (Lonza Biologics). Recombinant soluble ATR protein was expressed from 293T cells by transient transfection. Three days after transfection, conditioned media were collected and the ATR protein with a flag-tag at the carboxy terminus was purified from the media sample by passing it through an anti-flag monoclonal antibody affinity column (Sigma).

Preparation of PA Protein

PA protein was produced from a synthetic gene encoding the *B. anthracis* PA which was constructed using a combination of overlapping oligonucleotides and polymerase chain reaction (PCR). The synthetic gene encoding the *B. anthracis* PA residues E30-G764 of mature PA (SEQ ID NO:2) was codon-optimized for expression in the bacterium, *Escherichia coli*. Subsequent PCR amplification reactions were performed to add a heterologous signal peptide to the N-terminus of mature PA (E30-G764). PA was produced in *E. coli* K-12 cells and extracted from the cell paste upon periplasmic shock. The PA protein was purified using Q-sepharose-HP and hydroxyapatite chromatography. PA purity was confirmed by native- and SDS-PAGE silver staining, N-terminal protein sequencing, RP-HPLC and SEC-HPLC and was determined to be 96-98% pure.

To assess the proper function of the PA protein, the ability of the PA protein to form heptamers after enzymatic cleavage was evaluated. PA binds to its cell surface receptor and is cleaved by a furin-like protease to eliminate the N-terminal 20 kilodalton region. This cleavage permits the PA63 fragment to polymerize and form a heptameric pore in the membrane. PA63 can also be obtained in vitro by trypsin digestion (Benson et al, (1998) *Biochemistry* 37:3941-3948; Ahuja et al, (2001) *Biochem. Biophys. Res. Comm.* 286:6-11, each of which are herein incorporated by reference in their entireties). Purified PA (83 kilodaltons) was subjected to trypsin digestion to determine if the purified PA was capable of being cleaved to PA63 and if the cleaved PA63 fragments could form heptamers. The trypsin-treated PA protein was analyzed via SDS-PAGE and transferred to a membrane for protein sequencing. SDS-PAGE analysis indicated the trypsin-treated PA protein yielded a 63 kilodalton protein. Subsequent N-terminal sequence analysis confirmed the correct cleavage position. Moreover, native-PAGE analysis and mass spectrometry indicated that the 63 kilodalton subunits formed multimers. Heptameric PA63 was also captured on a Q-sepharose-HP column.

Inhibition of PA Binding to ATR Assay

The assay buffer for this assay consists of 1×PBS (pH 7.4, without calcium and magnesium; catalogue #17-516 from BioWhittaker), 2% BSA (Sigma, A-0336, stock 30% solution), 1 mM CaCl₂, 1 mM MgCl₂, 0.1% Tween-20. Calcium and magnesium need to be added to assay buffer at the time of assay. Biotinylated PA protein (final concentration 300 ng/ml; biotinylation was performed using EZ-Link™ Sulfo-NHS-LC-Biotin available from Pierce Biotechnology) is pre-incubated with antibody preparations (phage expressing scFv, purified scFv or whole antibody molecules, such as IgG molecules, comprising the VH and VL domains of specific scFvs) in assay buffer for 45 minutes, at room temperature with gentle shaking. Flag-tagged ATR protein (amino acids 1-227 of SEQ ID NO:3) is then added to the mixture and incubated for an additional 20 minutes.

Next, 2.5 microliters of streptavidin coated beads (Dyna-beads M-280, Dynal Biotech) is added to each well along with anti-flag antibody (Sigma, catalogue #F3165) (1 microgram/milliliter final concentration) that has been labeled with ORI-TAG®. (IGEN International) according to the manufacturer's directions. The mixture is then incubated for 45 minutes at room temperature with gentle shaking. Electrochemiluminescence is then measured using the M8 ECL unit (IGEN, International).

The protein concentrations given in the above-described assay can be modified by one of skill in the art to optimize assay performance, as necessary. Additionally, this assay may be modified to test an antibody's ability to block binding of PA to its receptor on other primary cells or cell lines, such as macrophage cell lines.

FIG. 1 shows results for the ability of antibodies PWD0283 and PWD0587 to inhibit the binding of biotinylated PA to ATR.

Inhibition of PA binding to CMG2

In an assay similar to the one described above antibody PWD0587 was tested for its ability to block binding of PA to a flag tagged version of CMG2 protein that also acts as an anthrax receptor (see, Scobie et al., (2003) *Proceedings of the National Academy of Sciences* 1.00:5170-5174). The CMG2 protein used consisted of amino acids 33-318 of SEQ ID NO:42 fused to a flag tag (SEQ ID NO:43). Using this assay, it was shown that an IgG1 format of the PWD0587 antibody also inhibits the binding of PA to CMG2.

Example 4

Detection of Biotinylated PA Binding to PA Receptor by Flow Cytometry

In preparation for a series of in vitro studies to test if anti-PA monoclonal antibodies of the invention can inhibit the action of PA, flow cytometry analysis of binding of biotinylated PA protein to CHO-K1 cells, J774A.1 cells, and human macrophages was performed. CHO-K1 cells are a cell line that have functional ATR protein on their surface. Both the J774A.1 cells (a murine macrophage cell line) and human macrophages also possess PA binding proteins on their surface. For flow cytometry analysis, PA protein was biotinylated as described above (Example 3) and added to cells in culture and incubated for 10-20 minutes at room temperature. The cells were washed and pelleted by centrifugation. Streptavidin PE was then added to the cell pellets and incubated briefly at room temperature. After washing, the cells were first resuspended in propidium iodide to discriminate between live and dead cells, and then were analyzed on a

FACScan. Data were acquired and analyzed using CellQuest software (Becton Dickinson). As shown in FIG. 2, biotinylated PA binds specifically to CHO-K1 cells, J774A.1 murine macrophages, and human macrophages, indicating that these cells have ATR protein on their surface.

Example 5

⁸⁶Rubidium Release Assay

PA has been shown to interact with the ATR on CHO-K1 cells (Escuyer and Collier, (1991) *Infect. Immunol.* 59:3381-3386, which is hereby incorporated by reference in its entirety. Following binding of PA to the ATR, a 20 kilodalton peptide is cleaved from the PA and the remaining PA63 molecules aggregate into heptamers and form a pore on the cell surface. One assay that has been developed to measure PA63-mediated pore formation monitors the release of intracellular ⁸⁶Rubidium (⁸⁶Rb) from cells that have been pre-loaded with ⁸⁶Rb. The following protocol may be used to test whether an antibody is able to inhibit the ability of PA63 to form pores in membranes.

⁸⁶Rubidium Release Assay Using CHO-K1 Cells

2.0×10⁵ CHO-K1 cells (ATCC#CCL 61, which express PA Receptor on their surface, see Example 4) are plated in a 24 well plate in 1 milliliter of culture medium (Ham's F12K medium with 2 mM L-glutamine adjusted to contain 2.5 g/L sodium bicarbonate, 90%; fetal bovine serum, 10%). The cells are incubated for 24 hours at 37° C., 5% CO₂. Medium is aspirated and replaced with milliliter of fresh culture medium containing ⁸⁶Rb at a concentration 1 microCurie/milliliter. Cells are incubated on ice for 30 minutes after which the medium is removed and the cells are washed two times with 750 µl of cold PBS. Next, 1 milliliter of medium containing PA alone or PA which has been pre-incubated (for 1 hour at 37 degrees on a rotator) with anti-PA antibody is added to the cells which are then incubated for 1.5 hours on ice. At the end of the incubation period, the cells are again washed twice with 750 µl of cold PBS. 500 microliters of cold MES-gluconate buffer, pH4.9 is then added and incubated on ice for 30 minutes. 100 microliters of supernatant is removed from cell supernatant and added to 2.0 ml of Supermix OptiPhase scintillant (Perkin-Elmer Life Sciences) and the radioactivity is counted using a Wallac Microbeta TRILUX Liquid Scintillation and Luminescence Counter (Perkin-Elmer). Radioactivity in the medium is indicative of pore formation by PA63.

To determine the optimal amount of PA to use in the ⁸⁶Rb release assay, PA was titrated by measuring ⁸⁶Rb release with different concentrations of PA (18, 6, 2, 0.67, 0.22, 0.074, 0.025, and 0 nM) were added to the assay. Based on this titration, 5 nM PA was chosen for the subsequent assays.

In this assay PATD, a mutant of PA which is defective in pore formation is used as a positive control for inhibition of pore formation. PATD is identical to wildtype PA with the exception that it has two amino acid mutations, K426D and D454K using the numbering of SEQ ID NO:2. PATD is described in Sellman et al., *J. Biol. Chem.* (2001), 276:8371-6, Sellman et al., *Science* 292:695-697, and in International Patent Publication WO01/82788 each of which is hereby incorporated by reference in its entirety.

FIG. 3 shows the ability of two antibodies PWD0283 and PWD0587 in whole IgG1 format to inhibit pore formation by PA protein using the above described assay.

⁸⁶Rubidium Release Assay Using Human Macrophages

The systemic shock and death from anthrax results primarily from the effects of high levels of cytokines produced by and released from macrophages that have been affected by the anthrax lethal toxin. Consequently, it was of interest to evaluate whether anti-PA antibodies of the invention could inhibit PA-mediated release of ⁸⁶Rb from human macrophages.

Preparation of Human Macrophages

For the preparation of human macrophages, peripheral blood mononuclear cells (PBMC) were isolated from various human donors by Ficoll-Hypaque density gradient centrifugation. PBMC were incubated with anti-CD14-labeled paramagnetic microbeads (Milenyi Biotec). After magnetic labeling, the cells were passed through a separation column placed in a strong permanent magnet. The magnetically-labeled cells retained in the column were then eluted, washed, and counted. CD14+ cells were then placed in 6-well culture dishes for 10-12 days in medium containing granulocyte-macrophage colony-stimulating factor (GM-CSF). Medium was replenished every 3 days until the cells were used in the assay.

Inhibition of ⁸⁶Rb Release from Human Macrophages by Anti-PA Monoclonal Antibodies

The ⁸⁶Rb release assay was performed as described above, except for using human macrophages in place of the CHO-K₁ cells. Anti-PA monoclonal antibodies PWD0283 and PWD0587 fully inhibited PA-mediated ⁸⁶Rb release at antibody concentration of about 5 nM.

Example 6**Identification and Cloning of VH and VL Domains**

One method to identify and clone VH and VL domains from cell lines expressing a particular antibody is to perform PCR with VH and VL specific primers on cDNA made from the antibody expressing cell lines. Briefly, RNA is isolated from the cell lines and used as a template for RT-PCR designed to amplify the VH and VL domains of the antibodies expressed by the EBV cell lines. Cells may lysed in the TRIzol® reagent (Life Technologies, Rockville, MD) and extracted with one fifth volume of chloroform. After addition of chloroform, the solution is allowed to incubate at room temperature for 10 minutes, and the centrifuged at 14,000 rpm for 15 minutes at 4° C. in a tabletop centrifuge. The supernatant is collected and RNA is precipitated using an equal volume of isopropanol. Precipitated RNA is pelleted by centrifuging at 14,000 rpm for 15 minutes at 4° C. in a tabletop centrifuge. Following centrifugation, the supernatant is discarded and washed with 75% ethanol. Following washing, the RNA is centrifuged again at 800 rpm for 5 minutes at 4° C. The supernatant is discarded and the pellet allowed to air dry. RNA is dissolved in DEPC water and heated to 60° C. for 10 minutes. Quantities of RNA can be determined using optical density measurements.

cDNA may be synthesized, according to methods well-known in the art, from 1.5-2.5 micrograms of RNA using reverse transcriptase and random hexamer primers. cDNA is then used as a template for PCR amplification of VH and VL domains. Primers used to amplify VH and VL genes are shown in Table 6. Typically a PCR reaction makes use of a single 5' primer and a single 3' primer. Sometimes, when the amount of available RNA template is limiting, or for greater efficiency, groups of 5' and/or 3' primers may be used. For example, sometimes all five VH-5' primers and all JH3' primers are used in a single PCR reaction. The PCR reaction is

carried out in a 50 microliter volume containing 1xPCR buffer, 2 mM of each dNTP, 0.7 units of High Fidelity Taq polymerase, 5' primer mix, 3' primer mix and 7.5 microliters of cDNA. The 5' and 3' primer mix of both VH and VL can be made by pooling together 22 pmole and 28 pmole, respectively, of each of the individual primers. PCR conditions are: 96° C. for 5 minutes; followed by 25 cycles of 94° C. for 1 minute, 50° C. for 1 minute, and 72° C. for 1 minute; followed by an extension cycle of 72° C. for 10 minutes. After the reaction is completed, sample tubes were stored 4° C.

TABLE 5

Primer Sequences Used to Amplify VH and VL domains.

Primer name	SEQ ID NO	Primer Sequence (5'-3')
VH Primers		
Hu VH1-5'	6	CAGGTGCAGCTGGTGCAGTCTGG
Hu VH2-5'	7	CAGGTCAACTTAAGGGAGTCTGG
Hu VH3-5'	8	GAGGTGCAGCTGGTGCAGTCTGG
Hu VH4-5'	9	CAGGTGCAGCTGCAGGAGTCCGGG
Hu VH5-5'	10	GAGGTGCAGCTGTTGCAGTCTGC
Hu VH6-5'	11	CAGGTACAGCTGCAGCAGTCAGG
Hu JH1-2-5'	12	TGAGGAGACGGTGACACGGGTGCC
Hu JH3-5'	13	TGAAGAGACGGTGACCATTTGTCCC
Hu JH4-5-5'	14	TGAGGAGACGGTGACACGGGTTC
Hu JH6-5'	15	TGAGGAGACGGTGACCGTGGTCCC
VL Primers		
Hu Vkappa1-5'	16	GACATCCAGATGACCCAGTCTCC
Hu Vkappa2a-5'	17	GATGTTGTGATGACTCAGTCTCC
Hu Vkappa2b-5'	18	GATATTGTGATGACTCAGTCTCC
Hu Vkappa3-5'	19	GAAATTGTGTTGACGCAGTCTCC
Hu Vkappa4-5'	20	GACATCGTGATGACCCAGTCTCC
Hu Vkappa5-5'	21	GAAACGACACTCAGCAGTCTCC
Hu Vkappa6-5'	22	GAAATTGTGCTGACTCAGTCTCC
Hu Vlambda1-5'	23	CAGTCTGTGTTGACGCAGCCGCC
Hu Vlambda2-5'	24	CAGTCTGCCCTGACTCAGCCTGC
Hu Vlambda3-5'	25	TCCTATGTGCTGACTCAGCCACC
Hu Vlambda3b-5'	26	TCTTCTGAGCTGACTCAGGACCC
Hu Vlambda4-5'	27	CACGTTATACTGACTCAACCGCC
Hu Vlambda5-5'	28	CAGGCTGTGCTCACTCAGCCGTC
Hu Vlambda6-5'	29	AATTTTATGCTGACTCAGCCCA
Hu Jkappa1-3'	30	ACGTTTGAATTCACCTTGGTCCC
Hu Jkappa2-3'	31	ACGTTTGAATTCACCTTGGTCCC
Hu Jkappa3-3'	32	ACGTTTGAATTCACCTTGGTCCC
Hu Jkappa4-3'	33	ACGTTTGAATTCACCTTGGTCCC
Hu Jkappa5-3'	34	ACGTTTGAATTCACCTTGGTCCC
Hu Jkappa6-3'	35	ACGTTTGAATTCACCTTGGTCCC
Hu Jkappa7-3'	36	ACGTTTGAATTCACCTTGGTCCC
Hu Jkappa8-3'	37	ACGTTTGAATTCACCTTGGTCCC
Hu Jkappa9-3'	38	ACGTTTGAATTCACCTTGGTCCC
Hu Jkappa10-3'	39	ACGTTTGAATTCACCTTGGTCCC
Hu Jkappa11-3'	40	ACGTTTGAATTCACCTTGGTCCC
Hu Jkappa12-3'	41	ACGTTTGAATTCACCTTGGTCCC

PCR samples are then electrophoresed on a 1.3% agarose gel. DNA bands of the expected sizes (~506 base pairs for VH domains, and 344 base pairs for VL domains) can be cut out of the gel and purified using methods well known in the art. Purified PCR products can be ligated into a PCR cloning vector (TA vector from Invitrogen Inc., Carlsbad, Calif.). Individual cloned PCR products can be isolated after transfection of *E. coli* and blue/white color selection. Cloned PCR products may then be sequenced using methods commonly known in the art.

Example 7**Kinetics of PA Binding Analyzed by Biacore**

For BLAcore analysis, PA and PA heptamer were immobilized on individual flow cells of a BLAcore CM5 sensor

chip. The PA monoclonal antibodies, PWD0283 and PWD0587 (IgG1 format), were diluted from 50 µg/mL (333 nM) to 0.625 µg/mL (4.1 nM). Each concentration was in contact with the PA proteins during a 4-minute association phase. The off-rate of the anti-PA monoclonal antibodies was determined by washing the complex in the presence of buffer for 5 minutes. The binding data were analyzed using the BIAevaluation software, Version 3.1. The kinetics of anti-PA monoclonal antibody binding to PA and to PA heptamer are summarized in Tables 6 and 7, respectively. Both PWD0283 and PWD0587 antibodies showed high affinity binding to both PA and its heptamer.

TABLE 6

Kinetics of anti-PA monoclonal antibody binding to PA			
Anti-PA mAb	ka (1/Ms)	kd (1/s)	KD (M)
PWD0283	4.46×10^6	1.03×10^{-3}	2.32×10^{-10}
PWD0587	2.44×10^5	5.30×10^{-4}	2.17×10^{-9}

ka (1/Ms, association rate constant; kd (1/s), dissociation rate constant; KD (M)

TABLE 7

Kinetics of anti-PA monoclonal antibody binding to PA heptamer			
Anti-PA mAb	ka (1/Ms)	kd (1/s)	KD (M)
PWD0283	2.28×10^6	4.26×10^{-4}	1.87×10^{-10}
PWD0587	3.23×10^5	6.50×10^{-5}	2.01×10^{-10}

ka (1/Ms, association rate constant; kd (1/s), dissociation rate constant; KD (M)

Example 8

Inhibition of Lethal Toxin Mediated Cell Killing by Anti-PA Antibodies

The ability of anti-PA antibodies to inhibit cell killing caused by lethal toxin (PA/LF) was evaluated using J774A.1, murine macrophage cell line (Quinn et al, (1991) *J Biol. Chem.* 266:20124-20130, herein incorporated by reference in its entirety). The cells were seeded in a 96-well micro titer plate and incubated overnight. The next day, fresh medium containing 100 ng/mL PA was added. Then, 20 µL of DMEM (containing 100 ng/mL PA) and 50 ng/mL LF was added. Cells were incubated for 3 hrs. To detect viable cells after lethal toxin treatment, 20 µL of CellTiter 96 AQueous One Solution Reagent (Promega) was added to each well and cells were incubated for 2.5 hrs. Plates were then read at 490 nm using SpectraMax250 (Molecular Devices). CellTiter 96 AQueous One Solution Reagent contains a tetrazolium compound which is bioreduced by metabolically active cells into a soluble colored formazan product. The quantity of formazan product as measured by absorbance at 490 nm is directly proportional to the number of living cells.

The ability of PA mAb, PWD0283 and PWD0587, to inhibit cell killing was compared with a negative control IgG1 mAb (CAT002). As shown in FIG. 4, PWD0283 and PWD0587 both inhibited lethal toxin-induced cell killing in a dose-dependent manner.

Prophylactic Use of Anti-PA Antibodies

Fisher 344 rats are highly susceptible to the lethal effects of systemic doses of lethal toxin (Sellman et al., (2001) *Science* 292:695-697 and Ivins et al., (1989) *Applied and Environmental Microbiology* 55:2098-2100, both of which are herein incorporated by reference in their entirety). Lethal toxin is the combination of the receptor-binding component, PA and the metalloprotease, LF, of *B. anthracis*. The following studies were performed to examine the ability of anti-PA antibodies to act prophylactically by intravenous (IV), subcutaneous (SC) or intramuscular (IM) administration when administered at various times before single or multiple injections of lethal toxin (also referred to as "PA/LF" in this example and Example 10). In these studies, the time to morbidity (TTM) was measured and the number of animals surviving at 24 hours were counted. The average TTM following injection of lethal toxin is approximately 90 minutes. Animals that survived past 24 hours were euthanized.

PA (83 kilodaltons) was formulated at a concentration of 0.45 mg/mL in a buffer containing 50 mM NaPO₄ and then diluted with phosphate-buffered normal saline to concentrations of 0.1125 mg/mL and 0.2 mg/mL. A volume of 0.2 mL delivered 0.0225 mg or 0.04 mg of PA. Doses of 0.09 mg/kg or 0.16 mg/kg were used. The dose 0.09 mg/kg was based on the lowest concentration needed to produce 100% lethality. The doses of PA monoclonal antibody and control monoclonal antibody used were in 10-fold molar excess of the PA dose.

Recombinant lethal factor (LF) from *B. anthracis*; List Biological Laboratories, Inc. (408.866.6363); Lot 1721B was provided as a lyophilized powder. When reconstituted with 1 mL sterile water for injection, the solution contained 1.0 mg LF in a buffer of 5 mM HEPES and 50 mM NaCl. It was then diluted with phosphate-buffered normal saline to a concentration of 0.040 mg/mL. A volume of 0.2 mL delivered 0.008 mg of LF. A dose of 0.032 mg/kg was used. This dose was based on the lowest concentration needed to produce 100% lethality.

Prophylactic Study 1: IV Administration of Anti-PA Antibodies 60 Minutes Prior to Injection of Lethal Toxin

In this study, the effects of PA mAb administered 60 minutes prior to a single, intravenous injection of PA/LF were examined. Male Fisher 344 rats (n=5/treatment) were assigned to the groups shown in Table 8. Sixty minutes before intravenous injection of PA/LF, animals received either anti-PA monoclonal antibodies (PWD0283 or PWD0587 in IgG1 format), a negative IgG1 control monoclonal antibody (CAT002), vehicle, or no study agent by intravenous injection.

As shown in Table 8 and FIG. 5, a single intravenous injection of PWD0283 or PWD0587 60 minutes prior to injection of lethal toxin provided 100% survival at 24 hours with no apparent ill effects. In contrast, a single injection of the negative control mAb, CAT002, provided no protection with 0% survival and an average TTM of 100 minutes. Vehicle or no study agent also provided no protection with 0% survival and an average TTM of 99 minutes and 91 minutes, respectively. In a separate study, rats receiving mAb alone without PA/LF showed no adverse effects.

TABLE 8

Group	n	Time of Study Agent relative to PA/LF (min)	Study Agent (3 mg/kg)	PA (mg/kg)	LF (mg/kg)	% Survival	TTM (minutes)
1	5	-60	PWD0283	0.16	0.032	100	—
2	5	-60	PWD0587	0.16	0.032	100	—
3	5	-60	CAT002	0.16	0.032	0	100
4	5	-60	vehicle	0.16	0.032	0	99
5	5	—	—	0.16	0.032	0	91

Prophylactic Study 2: SC and IM Administration of Anti-PA Antibodies 60 Minutes Prior to Injection of Lethal Toxin

Because intravenous administration of anti-PA antibodies given 1 hour prior to lethal toxin was completely protective against lethal toxin, the experiment was repeated giving the anti-PA antibodies by SC or IM administration 60 minutes prior to the lethal toxin to examine these routes of PA mAb administration. Male Fisher 344 rats (n=5/treatment) were assigned to the groups shown in Table 9. Sixty minutes before administration of PA/LF, animals received either PA mAb (PWD0283 or PWD0587), or a negative control antibody (CAT002).

SC administration of PWD0283 or PWD0587 (Table 9) 1 hour prior to lethal toxin administration provided no protection with 0% survival and an average TTM of 105 minutes and 145 minutes, respectively. IM administration of PWD0283 or PWD0587 (Table 9) 1 hour prior to lethal toxin administration provided 80% survival. The TTM's of the non-surviving animals were 240 minutes and 124 minutes, respectively, for the anti-PA monoclonal antibodies. Administration of CAT002 by either route of administration as a negative control provided no protection against the lethal effects of systemic lethal toxin. All rats in the route-matched control groups exhibited the expected SYMPTOMS of animals exposed to toxic levels of PA/LF. TTM in the control animals ranged from 85 to 93 minutes.

Prophylactic Study 3: IV, SC and IM Administration of Anti-PA Antibodies 24 Hours Prior to Injection of Lethal Toxin

Because administration of anti-PA antibodies given SC or IM 1 hour prior to lethal toxin was only partially protective, the experiment was repeated giving the anti-PA antibodies 24 hours prior to the lethal toxin, to allow the antibody more time to distribute in the animals. In this study, anti-PA antibodies were administered by SC, IM or IV injection 24 hours prior to a single intravenous injection of PA/LF. Male Fisher 344 rats (n=5/treatment) were assigned to the groups shown in Table 10. Twenty-four hours before administration of PA/LF, animals received either PA mAb (PWD0283 or PWD0587), or a negative control mAb (CAT002).

As shown in Table 10, a single SC, IM or IV injection of PWD0283 or PWD0587 24 hours prior to injection of lethal toxin provided 100% survival at 24 hours with no apparent ill effects. In contrast, a single injection of the negative control mAb, CAT002, regardless of route of administration, provided no protection with 0% survival and an average TTM of

TABLE 9

Group	N	Time of Study Agent relative to PA/LF (min)	Study Agent (3 mg/kg)	Route of Administration	PA (mg/kg)	LF (mg/kg)	% Survival	TTM (minutes)
1	5	-60	PWD0283	SC	0.09	0.032	0	145
2	5	-60	PWD0283	IM	0.09	0.032	80	240
3	5	-60	PWD0587	SC	0.09	0.032	0	105
4	5	-60	PWD0587	IM	0.09	0.032	80	124
5	5	-60	CAT002	SC	0.09	0.032	0	85
6	5	-60	CAT002	IM	0.09	0.032	0	93

100 minutes. In a separate study, rats receiving anti-PA antibodies alone without PA/LF showed no adverse effects.

TABLE 10

Group	N	Time of Study Agent relative to PA/LF (min)	Study Agent (3 mg/kg)	Route of Administration	PA (mg/kg)	LF (mg/kg)	% Survival	TTM (minutes)
1	5	-24	PWD0283	SC	0.09	0.032	100	—
2	5	-24	PWD0283	IM	0.09	0.032	100	—
3	5	-24	PWD0283	IV	0.09	0.032	100	—
4	5	-24	PWD0587	SC	0.09	0.032	100	—
5	5	-24	PWD0587	IM	0.09	0.032	100	—
6	5	-24	PWD0587	IV	0.09	0.032	100	—
7	5	-24	CAT002	SC	0.09	0.032	0	88

TABLE 10-continued

Group	N	Time of Study Agent relative to PA/LF (min)	Study Agent (3 mg/kg)	Route of Administration	PA (mg/kg)	LF (mg/kg)	% Survival	TTM (minutes)
8	5	-24	CAT002	IM	0.09	0.032	0	90
9	5	-24	CAT002		0.09	0.032	0	92

Prophylactic Study 4: Duration of Protective Effect of a Single IV Administration of Anti-PA Antibodies Against Multiple Lethal Toxin Challenge

The previous studies established that prophylactic administration of PWD0587 and PWD0283 protected Fisher 344 rats exposed to a lethal dose of anthrax toxin. The following study was designed to establish if administration of anti-PA antibodies would provide protection with recurrent multi-day administrations of lethal toxin.

Male Fisher 344 Rats (F344) were randomly assigned to groups of 5 as shown in Table 11. One injection of PWD0283 or PWD0587 was injected intravenously 1 hour prior to the first PA/LF injection on Day 1. The dose of antibody administered was approximately 10-fold higher than the PA in a single dose of lethal toxin on a molar basis. To provide sufficient control animals for the duration of the experiment 65 rats received CAT002 on Day 1. To assure lethality of the toxin, 5 rats from the CAT002 group were dosed each day parallel to the dosing of the PA mAb groups. Lethal toxin was administered on subsequent days to the animals surviving from the previous day. This study reports the data for 11 injections of lethal toxin through 15 days.

On Day 1, a single injection of PWD0283 or PWD0587 60 minutes prior to injection of lethal toxin provided 100% survival, replicating the results observed in the previous studies. Moreover, the single injection of PWD0283 or PWD0587 continued to provide 100% protection after 11 subsequent lethal toxin injections over 15 days (Table 11). Administration of the negative control mAb, CAT002, provided no protection (0% survival) in any of the day-matched control groups. The TTM in the day-matched controls ranged from 79 to 113 minutes.

Prophylactic Study 5: Protective Duration of Single IV Administration of Anti-PA Monoclonal Antibodies

The following study was designed to establish the duration of time which a single IV administration of anti-PA antibody would be protective against a single lethal toxin challenge.

Male Fisher 344 Rats (F344) were randomly assigned to groups of 5. Three, seven or fourteen days prior to PA/LF challenge, rats were given a single IV administration of PWD0283. Alternatively, seven, fourteen or twenty-one days prior to PA/LF challenge, rats were given a single IV administration of PWD0587. The dose of antibody administered was 1.5 mg/kg, which is approximately 10-fold higher than the PA in a single dose of lethal toxin on a molar basis. Control rats were given the an isotype-matched, non-PA-binding, control antibody (CAT002). PWD0283 fully protected (100% survival) rats from PA/LF when given three days prior to lethal toxin challenge, and protected 60% of animals (as measured 24 hours following PA/LF challenge) when administered seven days prior to challenge. Administration of PWD0283 14 days prior to PA/LF challenge was not protective. PWD0587 fully protected (100% survival) rats from PA/LF (as measured 24 hours following PA/LF challenge) when administered seven, fourteen or twenty-one days prior to challenge. Control antibody was not protective at any time point.

Together, the results of prophylactic studies 4 and 5 demonstrate that in addition to being protective against single or multiple challenges of PA/LF, the antibodies of the present invention are useful, for example, as passive immunotherapy, until such time as an individual can develop endogenous protective anti-PA antibody titers through vaccination or infection.

TABLE 11

Group	N	Time of Study Agent relative to PA/LF (min)	Study Agent (3 mg/kg)	Route of Administration	PA (mg/kg)	LF (mg/kg)	Day/No. of PA/LF challenges	% Survival	TTM (minutes)
1	5	-24	PWD0283	IV	0.09	0.032	15/11	100	—
2	5	-24	PWD0587	IV	0.09	0.032	15/11	100	—
3	65	-24	CAT002	IV	0.09	0.032	15/1*	0	79-113

*Each set of 5 rats in Group 3, only received 1 challenge

Importantly, this study does not establish the maximum duration of the protective effect. Furthermore, repeated administration of PA/LF may have allowed the animals to develop their own protective immune response against PA. Indeed, daily administration of PA only, but not of LF only, for 14 consecutive days, allows rats to survive a PA/LF challenge at day 14 (data not shown). This result is likely explained by the rats' generation of endogenous protective titers of neutralizing anti-PA antibodies.

Example 10

Dose Response of Prophylactic Monoclonal Antibody Treatment

Using the experimental approach defined in Example 8, Prophylactic Study I (with the exception that 0.09 mg/kg, rather than 0.16 mg/kg, of PA was injected in the PA/LF injection), the quantity of anti-PA antibody administered was

titrated to determine the minimum amount of antibody that would be protective. It was determined that doses of antibody equal to 10x, 1x, 0.75x, and 0.5x the molarity of PA injected allowed for 100% survival of animals, as measured 24 hours post PA/LF challenge. That is, doses as little as 0.075 mg/kg (0.136 nanomoles) of either PWD0283 or PWD0587 were fully protective when the PA/LF challenge comprised 0.09 mg/kg of PA (0.0272 nanomoles) and 0.032 mg/kg of LF (0.089 nanomoles). Doses of PWD0283 and PWD0587 antibody at one-quarter the molarity (0.038 mg/kg) of PA injected allowed 80% and 60% of the animals challenged to survive at least 24 hours (n=5/group). Doses of antibody one-tenth the molarity (0.015 mg/kg) of PA injected were not protective, although TTM was slightly extended to approximately 150 minutes compared to animals injected with the control antibody, CAT002, where TTM was approximately 100 minutes.

Example 11

Efficacy of Anti-PA Monoclonal Antibody Against Aerosolized Anthrax in the Rabbit Model

The following study was designed to test the efficacy of an anti-PA antibody, administered as either a prophylactic or a therapeutic, of preventing or delaying death due to inhalational exposure to *Bacillus anthracis*.

New Zealand White Rabbits (2.5-3.5 kg from Covance, Inc.) were randomly assigned to six groups, each containing 12 animals evenly divided between male and female. Animals in each group were each challenged aerosol inhalation of anthrax spores, either after or prior to receiving anti-PA antibody or vehicle control. Group I was a control group that received no antibody treatment. Groups II-IV received a single prophylactic dose of 1, 5, 10, or 20 mg/kg of anti-PA antibody (PWD0587), respectively, administered subcutaneously 2 days prior to *B. anthracis* spore challenge. Group IV received a single therapeutic dose of 40 mg/kg of anti-PA antibody (PWD0587) administered intravenously one hour after *B. anthracis* spore challenge. Animals were exposed via aerosolization to a target dose of 100x LD₅₀ of *B. anthracis* spores. Post-exposure measurements indicated that animals were actually exposed to spore challenge dose of 196x LD₅₀.

Observations: Clinical observations were recorded twice daily from receipt of rabbits until death. Body weights were recorded twice pre-dose, at dosing and at necropsy (data not shown). Food consumption (ad libitum) was confirmed by visual inspection. All animals that died or were euthanized due to moribundity had gross necropsy performed and recorded.

Blood collection: Blood collections were taken on days -7, 7, and 14 for hematology and serum chemistry as well as for determination of serum PA protein and anti-PA Antibody levels (results not shown). Serum PA protein and anti-PA antibody levels were also determined for blood collections taken at days 1, 2 and 4 (data not shown). Bacteremia was determined at Days 2, 7, 14 and at death (see below).

Study Termination: 14 days post-challenge, following blood collection, surviving animals were euthanized and a complete necropsy was performed and recorded. Tissue samples from all deaths (scheduled or unscheduled) were collected from liver, lung, mediastinal lymph node, spleen, kidney and brain.

Results: The efficacy of the treatments was assessed in three ways. First, the number of animals surviving at least 14 days post-challenge was recorded. Second, if animals died within the two weeks post challenge, the time to death was

recorded. Third, the bacteremia of the blood at 2, 7 and 14 days post-challenge and at death was also assessed.

Results of this experiment are shown in FIG. 6 and Table 1 below. All statistical tests are 2-sided and performed at the 5% level of significance.

The percentage of animals surviving to 14 days post-challenge among the vehicle control and PA mAb treated groups were compared using the Fisher's exact test. The survival at 14 days post-challenge is significantly different among the vehicle control and PA mAb treated groups (p-value<0.0001, Table 1). Compared with the vehicle control group (survival at Day 14=0%), the survival at Day 14 is significantly higher in the 5.0 mg/kg sc group (42%, p-value 0.0373), in both 10 mg/kg sc and 20 mg/kg sc groups (83%, p-value<0.0001), and in the 40 mg/kg iv group (100%, p-value<0.0001).

TABLE 12

Summary of the survival at Day 14 among all rabbits
(N = 12 per group)

Treatment	Survivors	P-value vs. Control ^a
Vehicle	0 (0%)	
1 mg/kg sc	0 (0%)	NA
5 mg/kg sc	5 (42%)	0.0373
10 mg/kg sc	10 (83%)	<0.0001
20 mg/kg sc	10 (83%)	<0.0001
40 mg/kg iv	12 (100%)	<0.0001

^aobtained from a 2-sided Fisher's exact test. The p-values for the comparison among all groups are <0.0001; regardless of the inclusion or exclusion of the 40 mg/kg iv group in the analysis.

The Cochran-Armitage test was used to examine the dose response trend of the survival at 14 days post-challenge among the vehicle control and PA mAb sc treated groups. There is a significant dose-response trend with respect to the survival at day 14 (p-value<0.0001). The percentage of animals of surviving to day 14 increase significantly as the dose level of PA mAb (PWD 0587) increases.

The survival time from spore challenge to death was analyzed using a log-rank test. The survival time for the rabbits that survived at the end of follow-up is censored at the 14-day study period. The survival time of the rabbits is significantly different among the vehicle control and PA mAb treated groups (p-value<0.0001, FIG. 1). Compared with the vehicle control group (median survival time=2 days), the median survival times are 3 days in the 1 mg/kg sc group (p-value 0.0002), 6.5 days in the 5 mg/kg sc group (value<0.0001), and more than 14 days in the 10 mg/kg se, 20 mg/kg sc, and 40 mg/kg iv groups (all values<0.0001), respectively.

The incidence of bacteremia in blood samples was also analyzed (See Table 13).

TABLE 13

Number of Animals with Bacteremia at Day 2, Day 7 or at Death

Treatment	Day 2	Day 7 ^a	Death (see FIG. 6)
Vehicle	12/12	NA	11/12 animals died on Day 2; 1 animal survived to Day 3
1 mg/kg sc	0/12	NA	12/12 animals died prior to Day 7; 10/12 animals were bacteremic at death
5 mg/kg sc	0/12	0/5	7/12 animals died on or prior to Day 7. 5 of those 7 animals were bacteremic at death

TABLE 13-continued

Number of Animals with Bacteremia at Day 2, Day 7 or at Death			
Treatment	Day 2	Day 7 ^a	Death (see FIG. 6)
10 mg/kg sc	0/12	1/10	One animal died at day 6. A second animal died at day 7. Neither of these animals were bacteremic at death.
20 mg/kg sc	1/12 ^b	1/10	One animal died at day 5. A second animal died at day 7. One of the animals was bacteremic at death.
40 mg/kg iv	0/12	0/12	12/12 animals survived to Day 14. No bacteremia was observed in 12/12 animals.

^aBacteremia of surviving animals indicated.^bBacteremic animal at day 2 survived.

In summary, subcutaneous administration of anti-PA monoclonal antibody 2 days prior to lethal challenge with anthrax spores significantly prolongs time to death and/or increases the survival rate of challenged animals. Bacteremia was most often associated with found dead or moribund necropsied rabbits. Preliminary results showed no evidence of gross pathology at terminal necropsy.

Example 12

Cynomolgus Monkey Inhalation Spore Challenge Study

The following study was designed to examine the efficacy of an anti-PA monoclonal antibody, administered as a prophylactic treatment, against lethality due to inhalational exposure to *Bacillus anthracis* in cynomolgus monkeys.

40 cynomolgus monkeys were randomly assigned to four groups, each containing 10 animals. Animals in each group were each challenged via aerosol inhalation of anthrax spores, 2 days after receiving anti-PA antibody (PWD0587) at 10, 20 or 40 mg/kg or vehicle control. Animals were exposed via aerosolization to a target dose of 100× LD₅₀ of *B. anthracis* spores. Post-exposure measurements indicated that animals were actually exposed to spore challenge dose of 186× LD₅₀.

Statistical Methods

The primary efficacy endpoint is survival at Day 28 following spore challenge. Difference in 28-day survival between any one of the PA mAb treated groups and the vehicle control group are evaluated by 2-tailed Fisher's exact test. The secondary efficacy endpoint is survival time, defined as the time from spore challenge to death during the 28-day study. The Cochran-Armitage test is used to examine the dose response trend among the groups.

The survival time from spore challenge to death was analyzed using a log-rank test. The survival time for the monkeys that survived at the end of follow-up is censored at the 28-day study period. All statistical tests are 2-sided and performed at the 5% level of significance.

Results

FIG. 7 shows the percent survival of cynomolgus monkeys prophylactically treated with anti-PA monoclonal antibody PWD0587 (IgG1 format) and challenged with a lethal aerosolized dose of *B. anthracis* spores. Survival is significantly different among the vehicle control and PA mAb treated groups (P value=0.0002). Compared with the vehicle control group, survival is significantly higher in the 10 mg/kg group

(60%, P value=0.0108), the 20 mg/kg group (70%, P value=0.0031), and 40 mg/kg group (90%, P value=0.0001) (Table 14). There is a significant dose-response trend with respect to survival (P value=0.0002). The survival at Day 28 increases significantly as the dose level of PWD0587 increases.

TABLE 14

Survival in monkey study		
Treatment	Survivors	P Value vs. Control ^a
Vehicle	0 (0%)	
10 mg/kg	6 (60%)	0.0108
20 mg/kg	7 (70%)	0.0031
40 mg/kg	9 (90%)	0.0001

^aobtained from a 2-sided Fisher's exact test. The P value = 0.0002 for the comparison among all groups.

The survival time of the monkeys is significantly different among the vehicle control and PA mAb treated groups (P value<0.0001, FIG. 7). Compared with the vehicle control group (median survival time=4 days), the median survival times in all 3 PWD0587 treatment groups are significantly longer (more than 28 days; all P values≤0.0005), FIG. 7. None of the surviving PA mAb-treated animals had positive (bacteremic) blood cultures at Days 7, 14, or 21 or 28.

Example 13

Detection of Neutralizing Antibodies Against Anthrax Protective Antigen by Edema Factor-Mediated cAMP Induction Assay

As described above, antibodies that neutralize the biological activity of PA protein can be identified by using a rubidium release assay such as the one described in Example 5 and/or a lethal toxin mediated cell killing assay such as the one described in Example 8. An additional assay which can be used to identify neutralizing antibodies against PA is an edema factor-mediated cAMP induction assay. This bioassay is based upon the ability of edema factor, a bacterial adenylate cyclase dependent upon PA for entry into cells, to bind PA and enter cells leading to a measurable increase in cAMP. In the presence of antibodies that neutralize PA, edema factor (EF) is inhibited from entering cells and reduced cAMP levels are observed.

Briefly, cells expressing anthrax receptor are exposed to edema toxin (PA+EF). Levels of cAMP in the cells are measured by any method known in the art, for example by ELISA using an anti-cAMP antibody. The ability of an antibody to inhibit edema toxin mediated increases in intracellular levels of cAMP can be assayed by pre-incubating the edema toxin with a test antibody and then exposing the cells expressing anthrax receptor with the antibody/edema toxin mixture.

By way of non-limiting example, cAMP levels induced by edema factor, and the inhibition of same by anti-PA antibodies of the invention, can be measured using the following assay. 4000 Chinese Hamster Ovary cells in 100 microliters of CHO culture medium (CCM; F-12K growth medium (Invitrogen, Carlsbad, Calif.) supplemented with 10% fetal bovine serum, 100 units/ml penicillin and 100 micrograms/ml streptomycin) are seeded into cAMP-Direct ELISA plates (Applied Biosystems, Foster City, Calif.; Cat No. T1507). Cells are incubated at 37° C., 5% CO₂, greater than 85% relative humidity while test samples are prepared.

In a separate assay plate, test antibodies starting at a concentration of 60 micrograms/milliliter in CCM/IBMX (CCM

supplemented with 250 micromoles 3-isobutyl-1 methylxanthine) are diluted 3-fold for a total 10 serial dilutions in CCM/IBMX. 75 microliters of each dilution of antibody is then added to 75 microliters of PA/EF solution (1200 nanograms/milliliter PA and 100 nanograms/milliliter EF in CCM/IBMX). anti-PA/edema toxin mixture is incubated at 37° C., 5% CO₂ for one hour.

At the end of the hour, the cell culture medium supernatant from the cAMP-Direct ELISA plates onto which CHO cells have been plated (described above), is removed. Then 100 microliters of the anti-PA/edema toxin mixture is added to the wells containing the cells which are then incubated at 37° C., 5% CO₂ for one hour. At the end of the hour, the anti-PA/edema toxin mixture is removed and 60 microliters of lysis buffer is added to the cells. From this point forward, the cAMP-Direct ELISA is completed according to the manufacturer's instructions. In the absence of neutralizing antibody, cAMP levels induced by edema toxin are approximately 100-fold greater than that induced by controls (e.g. samples containing no EF).

It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing descrip-

tion and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

The entire disclosure of all publications (including patents, patent applications, journal articles, laboratory manuals, books, or other documents) cited herein are hereby incorporated by reference.

Further, the Sequence Listing submitted herewith, in both computer and paper forms, is hereby incorporated by reference in its entirety.

The entire disclosure (including the specification, sequence listing, and drawings) of each of U.S. Provisional Application Nos. 60/391,162, filed Jun. 26, 2002, 60/406,339, filed Aug. 28, 2002, 60/417,305, filed Oct. 10, 2002, 60/426,360, filed Nov. 15, 2002, 60/434,807, filed Dec. 20, 2002, 60/438,004, filed Jan. 6, 2003, 60/443,858 filed Jan. 31, 2003, 60/443,781, filed Jan. 31, 2003, 60/454,613 filed Mar. 17, 2003, and 60/468,651 filed May 8, 2003 is herein incorporated by reference in its entirety.

SEQUENCE LISTING

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Asn Ile Pro Ser Glu Asn Gln Tyr Phe Gln Ser Ala Ile Trp Ser Gly
          85           90           95

Phe Ile Lys Val Lys Lys Ser Asp Glu Tyr Thr Phe Ala Thr Ser Ala
          100          105          110

Asp Asn His Val Thr Met Trp Val Asp Asp Gln Glu Val Ile Asn Lys
115          120          125

Ala Ser Asn Ser Asn Lys Ile Arg Leu Glu Lys Gly Arg Leu Tyr Gln
130          135          140

Ile Lys Ile Gln Tyr Gln Arg Glu Asn Pro Thr Glu Lys Gly Leu Asp
145          150          155          160

Phe Lys Leu Tyr Trp Thr Asp Ser Gln Asn Lys Lys Glu Val Ile Ser
          165          170          175

Ser Asp Asn Leu Gln Leu Pro Glu Leu Lys Gln Lys Ser Ser Asn Ser
          180          185          190

Arg Lys Lys Arg Ser Thr Ser Ala Gly Pro Thr Val Pro Asp Arg Asp
          195          200          205

Asn Asp Gly Ile Pro Asp Ser Leu Glu Val Glu Gly Tyr Thr Val Asp
210          215          220

Val Lys Asn Lys Arg Thr Phe Leu Ser Pro Trp Ile Ser Asn Ile His
225          230          235          240

Glu Lys Lys Gly Leu Thr Lys Tyr Lys Ser Ser Pro Glu Lys Trp Ser
          245          250          255

Thr Ala Ser Asp Pro Tyr Ser Asp Phe Glu Lys Val Thr Gly Arg Ile
260          265          270

Asp Lys Asn Val Ser Pro Glu Ala Arg His Pro Leu Val Ala Ala Tyr
275          280          285

Pro Ile Val His Val Asp Met Glu Asn Ile Ile Leu Ser Lys Asn Glu
290          295          300

Asp Gln Ser Thr Gln Asn Thr Asp Ser Gln Thr Arg Thr Ile Ser Lys
305          310          315          320

Asn Thr Ser Thr Ser Arg Thr His Thr Ser Glu Val His Gly Asn Ala
          325          330          335

Glu Val His Ala Ser Phe Phe Asp Ile Gly Gly Ser Val Ser Ala Gly
          340          345          350

Phe Ser Asn Ser Asn Ser Ser Thr Val Ala Ile Asp His Ser Leu Ser
          355          360          365

Leu Ala Gly Glu Arg Thr Trp Ala Glu Thr Met Gly Leu Asn Thr Ala
370          375          380

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Asp Thr Ala Arg Leu Asn Ala Asn Ile Arg Tyr Val Asn Thr Gly Thr
385                      390                      395                      400

Ala Pro Ile Tyr Asn Val Leu Pro Thr Thr Ser Leu Val Leu Gly Lys
                      405                      410                      415

Asn Gln Thr Leu Ala Thr Ile Lys Ala Lys Glu Asn Gln Leu Ser Gln
                      420                      425                      430

Ile Leu Ala Pro Asn Asn Tyr Tyr Pro Ser Lys Asn Leu Ala Pro Ile
435                      440                      445

Ala Leu Asn Ala Gln Asp Asp Phe Ser Ser Thr Pro Ile Thr Met Asn
450                      455                      460

Tyr Asn Gln Phe Leu Glu Leu Glu Lys Thr Lys Gln Leu Arg Leu Asp
465                      470                      475                      480

Thr Asp Gln Val Tyr Gly Asn Ile Ala Thr Tyr Asn Phe Glu Asn Gly
485                      490                      495

Arg Val Arg Val Asp Thr Gly Ser Asn Trp Ser Glu Val Leu Pro Gln
500                      505                      510

Ile Gln Glu Thr Thr Ala Arg Ile Ile Phe Asn Gly Lys Asp Leu Asn
515                      520                      525

Leu Val Glu Arg Arg Ile Ala Ala Val Asn Pro Ser Asp Pro Leu Glu
530                      535                      540

Thr Thr Lys Pro Asp Met Thr Leu Lys Glu Ala Leu Lys Ile Ala Phe
545                      550                      555                      560

Gly Phe Asn Glu Pro Asn Gly Asn Leu Gln Tyr Gln Gly Lys Asp Ile
565                      570                      575

Thr Glu Phe Asp Phe Asn Phe Asp Gln Gln Thr Ser Gln Asn Ile Lys
580                      585                      590

Asn Gln Leu Ala Glu Leu Asn Ala Thr Asn Ile Tyr Thr Val Leu Asp
595                      600                      605

Lys Ile Lys Leu Asn Ala Lys Met Asn Ile Leu Ile Arg Asp Lys Arg
610                      615                      620

Phe His Tyr Asp Arg Asn Asn Ile Ala Val Gly Ala Asp Glu Ser Val
625                      630                      635                      640

Val Lys Glu Ala His Arg Glu Val Ile Asn Ser Ser Thr Glu Gly Leu
645                      650                      655

Leu Leu Asn Ile Asp Lys Asp Ile Arg Lys Ile Leu Ser Gly Tyr Ile
660                      665                      670

Val Glu Ile Glu Asp Thr Glu Gly Leu Lys Glu Val Ile Asn Asp Arg
675                      680                      685

Tyr Asp Met Leu Asn Ile Ser Ser Leu Arg Gln Asp Gly Lys Thr Phe
690                      695                      700

Ile Asp Phe Lys Lys Tyr Asn Asp Lys Leu Pro Leu Tyr Ile Ser Asn
705                      710                      715                      720

Pro Asn Tyr Lys Val Asn Val Tyr Ala Val Thr Lys Glu Asn Thr Ile
725                      730                      735

Ile Asn Pro Ser Glu Asn Gly Asp Thr Ser Thr Asn Gly Ile Lys Lys
740                      745                      750

Ile Leu Ile Phe Ser Lys Lys Gly Tyr Glu Ile Gly
755                      760

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<210> SEQ ID NO 3

<211> LENGTH: 368

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 3

-continued

Met Ala Thr Ala Glu Arg Arg Ala Leu Gly Ile Gly Phe Gln Trp Leu
 1 5 10 15
 Ser Leu Ala Thr Leu Val Leu Ile Cys Ala Gly Gln Gly Gly Arg Arg
 20 25 30
 Glu Asp Gly Gly Pro Ala Cys Tyr Gly Gly Phe Asp Leu Tyr Phe Ile
 35 40 45
 Leu Asp Lys Ser Gly Ser Val Leu His His Trp Asn Glu Ile Tyr Tyr
 50 55 60
 Phe Val Glu Gln Leu Ala His Lys Phe Ile Ser Pro Gln Leu Arg Met
 65 70 75 80
 Ser Phe Ile Val Phe Ser Thr Arg Gly Thr Thr Leu Met Lys Leu Thr
 85 90 95
 Glu Asp Arg Glu Gln Ile Arg Gln Gly Leu Glu Glu Leu Gln Lys Val
 100 105 110
 Leu Pro Gly Gly Asp Thr Tyr Met His Glu Gly Phe Glu Arg Ala Ser
 115 120 125
 Glu Gln Ile Tyr Tyr Glu Asn Arg Gln Gly Tyr Arg Thr Ala Ser Val
 130 135 140
 Ile Ile Ala Leu Thr Asp Gly Glu Leu His Glu Asp Leu Phe Phe Tyr
 145 150 155 160
 Ser Glu Arg Glu Ala Asn Arg Ser Arg Asp Leu Gly Ala Ile Val Tyr
 165 170 175
 Cys Val Gly Val Lys Asp Phe Asn Glu Thr Gln Leu Ala Arg Ile Ala
 180 185 190
 Asp Ser Lys Asp His Val Phe Pro Val Asn Asp Gly Phe Gln Ala Leu
 195 200 205
 Gln Gly Ile Ile His Ser Ile Leu Lys Lys Ser Cys Ile Glu Ile Leu
 210 215 220
 Ala Ala Glu Pro Ser Thr Ile Cys Ala Gly Glu Ser Phe Gln Val Val
 225 230 235 240
 Val Arg Gly Asn Gly Phe Arg His Ala Arg Asn Val Asp Arg Val Leu
 245 250 255
 Cys Ser Phe Lys Ile Asn Asp Ser Val Thr Leu Asn Glu Lys Pro Phe
 260 265 270
 Ser Val Glu Asp Thr Tyr Leu Leu Cys Pro Ala Pro Ile Leu Lys Glu
 275 280 285
 Val Gly Met Lys Ala Ala Leu Gln Val Ser Met Asn Asp Gly Leu Ser
 290 295 300
 Phe Ile Ser Ser Ser Val Ile Ile Thr Thr Thr His Cys Ser Asp Gly
 305 310 315 320
 Ser Ile Leu Ala Ile Ala Leu Leu Ile Leu Phe Leu Leu Leu Ala Leu
 325 330 335
 Ala Leu Leu Trp Trp Phe Trp Pro Leu Cys Cys Thr Val Ile Ile Lys
 340 345 350
 Glu Val Pro Pro Pro Pro Ala Glu Glu Ser Glu Glu Asn Lys Ile Lys
 355 360 365

<210> SEQ ID NO 4

<211> LENGTH: 800

<212> TYPE: PRT

<213> ORGANISM: Bacillus anthracis

<400> SEQUENCE: 4

Met Thr Arg Asn Lys Phe Ile Pro Asn Lys Phe Ser Ile Ile Ser Phe

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1	5	10	15
Ser Val	Leu Leu Phe Ala Ile Ser	Ser Ser Gln Ala Ile Glu Val Asn	
	20	25	30
Ala Met	Asn Glu His Tyr Thr Glu Ser Asp Ile Lys Arg Asn His Lys		
	35	40	45
Thr Glu	Lys Asn Lys Thr Glu Lys Glu Lys Phe Lys Asp Ser Ile Asn		
	50	55	60
Asn Leu	Val Lys Thr Glu Phe Thr Asn Glu Thr Leu Asp Lys Ile Gln		
	65	70	75
Gln Thr	Gln Asp Leu Leu Lys Lys Ile Pro Lys Asp Val Leu Glu Ile		
	85	90	95
Tyr Ser	Glu Leu Gly Gly Glu Ile Tyr Phe Thr Asp Ile Asp Leu Val		
	100	105	110
Glu His	Lys Glu Leu Gln Asp Leu Ser Glu Glu Glu Lys Asn Ser Met		
	115	120	125
Asn Ser	Arg Gly Glu Lys Val Pro Phe Ala Ser Arg Phe Val Phe Glu		
	130	135	140
Lys Lys	Arg Glu Thr Pro Lys Leu Ile Ile Asn Ile Lys Asp Tyr Ala		
	145	150	155
Ile Asn	Ser Glu Gln Ser Lys Glu Val Tyr Tyr Glu Ile Gly Lys Gly		
	165	170	175
Ile Ser	Leu Asp Ile Ile Ser Lys Asp Lys Ser Leu Asp Pro Glu Phe		
	180	185	190
Leu Asn	Leu Ile Lys Ser Leu Ser Asp Asp Ser Asp Ser Ser Asp Leu		
	195	200	205
Leu Phe	Ser Gln Lys Phe Lys Glu Lys Leu Glu Leu Asn Asn Lys Ser		
	210	215	220
Ile Asp	Ile Asn Phe Ile Lys Glu Asn Leu Thr Glu Phe Gln His Ala		
	225	230	235
Phe Ser	Leu Ala Phe Ser Tyr Tyr Phe Ala Pro Asp His Arg Thr Val		
	245	250	255
Leu Glu	Leu Tyr Ala Pro Asp Met Phe Glu Tyr Met Asn Lys Leu Glu		
	260	265	270
Lys Gly	Gly Phe Glu Lys Ile Ser Glu Ser Leu Lys Lys Glu Gly Val		
	275	280	285
Glu Lys	Asp Arg Ile Asp Val Leu Lys Gly Glu Lys Ala Leu Lys Ala		
	290	295	300
Ser Gly	Leu Val Pro Glu His Ala Asp Ala Phe Lys Lys Ile Ala Arg		
	305	310	315
Glu Leu	Asn Thr Tyr Ile Leu Phe Arg Pro Val Asn Lys Leu Ala Thr		
	325	330	335
Asn Leu	Ile Lys Ser Gly Val Ala Thr Lys Gly Leu Asn Val His Gly		
	340	345	350
Lys Ser	Ser Asp Trp Gly Pro Val Ala Gly Tyr Ile Pro Phe Asp Gln		
	355	360	365
Asp Leu	Ser Lys Lys His Gly Gln Gln Leu Ala Val Glu Lys Gly Asn		
	370	375	380
Leu Glu	Asn Lys Lys Ser Ile Thr Glu His Glu Gly Glu Ile Gly Lys		
	385	390	395
Ile Pro	Leu Lys Leu Asp His Leu Arg Ile Glu Glu Leu Lys Glu Asn		
	405	410	415
Gly Ile	Ile Leu Lys Gly Lys Lys Glu Ile Asp Asn Gly Lys Lys Tyr		
	420	425	430

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Tyr Leu Leu Glu Ser Asn Asn Gln Val Tyr Glu Phe Arg Ile Ser Asp
    435                      440                      445

Glu Asn Asn Glu Val Gln Tyr Lys Thr Lys Glu Gly Lys Ile Thr Val
    450                      455                      460

Leu Gly Glu Lys Phe Asn Trp Arg Asn Ile Glu Val Met Ala Lys Asn
    465                      470                      475                      480

Val Glu Gly Val Leu Lys Pro Leu Thr Ala Asp Tyr Asp Leu Phe Ala
    485                      490                      495

Leu Ala Pro Ser Leu Thr Glu Ile Lys Lys Gln Ile Pro Gln Lys Glu
    500                      505                      510

Trp Asp Lys Val Val Asn Thr Pro Asn Ser Leu Glu Lys Gln Lys Gly
    515                      520                      525

Val Thr Asn Leu Leu Ile Lys Tyr Gly Ile Glu Arg Lys Pro Asp Ser
    530                      535                      540

Thr Lys Gly Thr Leu Ser Asn Trp Gln Lys Gln Met Leu Asp Arg Leu
    545                      550                      555                      560

Asn Glu Ala Val Lys Tyr Thr Gly Tyr Thr Gly Gly Asp Val Val Asn
    565                      570                      575

His Gly Thr Glu Gln Asp Asn Glu Glu Phe Pro Glu Lys Asp Asn Glu
    580                      585                      590

Ile Phe Ile Ile Asn Pro Glu Gly Glu Phe Ile Leu Thr Lys Asn Trp
    595                      600                      605

Glu Met Thr Gly Arg Phe Ile Glu Lys Asn Ile Thr Gly Lys Asp Tyr
    610                      615                      620

Leu Tyr Tyr Phe Asn Arg Ser Tyr Asn Lys Ile Ala Pro Gly Asn Lys
    625                      630                      635                      640

Ala Tyr Ile Glu Trp Thr Asp Pro Ile Thr Lys Ala Lys Ile Asn Thr
    645                      650                      655

Ile Pro Thr Ser Ala Glu Phe Ile Lys Asn Leu Ser Ser Ile Arg Arg
    660                      665                      670

Ser Ser Asn Val Gly Val Tyr Lys Asp Ser Gly Asp Lys Asp Glu Phe
    675                      680                      685

Ala Lys Lys Glu Ser Val Lys Lys Ile Ala Gly Tyr Leu Ser Asp Tyr
    690                      695                      700

Tyr Asn Ser Ala Asn His Ile Phe Ser Gln Glu Lys Lys Arg Lys Ile
    705                      710                      715                      720

Ser Ile Phe Arg Gly Ile Gln Ala Tyr Asn Glu Ile Glu Asn Val Leu
    725                      730                      735

Lys Ser Lys Gln Ile Ala Pro Glu Tyr Lys Asn Tyr Phe Gln Tyr Leu
    740                      745                      750

Lys Glu Arg Ile Thr Asn Gln Val Gln Leu Leu Leu Thr His Gln Lys
    755                      760                      765

Ser Asn Ile Glu Phe Lys Leu Leu Tyr Lys Gln Leu Asn Phe Thr Glu
    770                      775                      780

Asn Glu Thr Asp Asn Phe Glu Val Phe Gln Lys Ile Ile Asp Glu Lys
    785                      790                      795                      800

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<210> SEQ ID NO 5

<211> LENGTH: 809

<212> TYPE: PRT

<213> ORGANISM: Bacillus anthracis

<400> SEQUENCE: 5

Met Asn Ile Lys Lys Glu Phe Ile Lys Val Ile Ser Met Ser Cys Leu

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1	5	10	15
Val Thr Ala Ile Thr Leu Ser Gly Pro Val Phe Ile Pro Leu Val Gln	20	25	30
Gly Ala Gly Gly His Gly Asp Val Gly Met His Val Lys Glu Lys Glu	35	40	45
Lys Asn Lys Asp Glu Asn Lys Arg Lys Asp Glu Glu Arg Asn Lys Thr	50	55	60
Gln Glu Glu His Leu Lys Glu Ile Met Lys His Ile Val Lys Ile Glu	65	70	75
Val Lys Gly Glu Glu Ala Val Lys Lys Glu Ala Ala Glu Lys Leu Leu	85	90	95
Glu Lys Val Pro Ser Asp Val Leu Glu Met Tyr Lys Ala Ile Gly Gly	100	105	110
Lys Ile Tyr Ile Val Asp Gly Asp Ile Thr Lys His Ile Ser Leu Glu	115	120	125
Ala Leu Ser Glu Asp Lys Lys Lys Ile Lys Asp Ile Tyr Gly Lys Asp	130	135	140
Ala Leu Leu His Glu His Tyr Val Tyr Ala Lys Glu Gly Tyr Glu Pro	145	150	155
Val Leu Val Ile Gln Ser Ser Glu Asp Tyr Val Glu Asn Thr Glu Lys	165	170	175
Ala Leu Asn Val Tyr Tyr Glu Ile Gly Lys Ile Leu Ser Arg Asp Ile	180	185	190
Leu Ser Lys Ile Asn Gln Pro Tyr Gln Lys Phe Leu Asp Val Leu Asn	195	200	205
Thr Ile Lys Asn Ala Ser Asp Ser Asp Gly Gln Asp Leu Leu Phe Thr	210	215	220
Asn Gln Leu Lys Glu His Pro Thr Asp Phe Ser Val Glu Phe Leu Glu	225	230	235
Gln Asn Ser Asn Glu Val Gln Glu Val Phe Ala Lys Ala Phe Ala Tyr	245	250	255
Tyr Ile Glu Pro Gln His Arg Asp Val Leu Gln Leu Tyr Ala Pro Glu	260	265	270
Ala Phe Asn Tyr Met Asp Lys Phe Asn Glu Gln Glu Ile Asn Leu Ser	275	280	285
Leu Glu Glu Leu Lys Asp Gln Arg Met Leu Ser Arg Tyr Glu Lys Trp	290	295	300
Glu Lys Ile Lys Gln His Tyr Gln His Trp Ser Asp Ser Leu Ser Glu	305	310	315
Glu Gly Arg Gly Leu Leu Lys Lys Leu Gln Ile Pro Ile Glu Pro Lys	325	330	335
Lys Asp Asp Ile Ile His Ser Leu Ser Gln Glu Glu Lys Glu Leu Leu	340	345	350
Lys Arg Ile Gln Ile Asp Ser Ser Asp Phe Leu Ser Thr Glu Glu Lys	355	360	365
Glu Phe Leu Lys Lys Leu Gln Ile Asp Ile Arg Asp Ser Leu Ser Glu	370	375	380
Glu Glu Lys Glu Leu Leu Asn Arg Ile Gln Val Asp Ser Ser Asn Pro	385	390	395
Leu Ser Glu Lys Glu Lys Glu Phe Leu Lys Lys Leu Lys Leu Asp Ile	405	410	415
Gln Pro Tyr Asp Ile Asn Gln Arg Leu Gln Asp Thr Gly Gly Leu Ile	420	425	430

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Asp Ser Pro Ser Ile Asn Leu Asp Val Arg Lys Gln Tyr Lys Arg Asp
  435                               440               445

Ile Gln Asn Ile Asp Ala Leu Leu His Gln Ser Ile Gly Ser Thr Leu
  450                               455               460

Tyr Asn Lys Ile Tyr Leu Tyr Glu Asn Met Asn Ile Asn Asn Leu Thr
  465                               470               475               480

Ala Thr Leu Gly Ala Asp Leu Val Asp Ser Thr Asp Asn Thr Lys Ile
  485                               490               495

Asn Arg Gly Ile Phe Asn Glu Phe Lys Lys Asn Phe Lys Tyr Ser Ile
  500                               505               510

Ser Ser Asn Tyr Met Ile Val Asp Ile Asn Glu Arg Pro Ala Leu Asp
  515                               520               525

Asn Glu Arg Leu Lys Trp Arg Ile Gln Leu Ser Pro Asp Thr Arg Ala
  530                               535               540

Gly Tyr Leu Glu Asn Gly Lys Leu Ile Leu Gln Arg Asn Ile Gly Leu
  545                               550               555               560

Glu Ile Lys Asp Val Gln Ile Ile Lys Gln Ser Glu Lys Glu Tyr Ile
  565                               570               575

Arg Ile Asp Ala Lys Val Val Pro Lys Ser Lys Ile Asp Thr Lys Ile
  580                               585               590

Gln Glu Ala Gln Leu Asn Ile Asn Gln Glu Trp Asn Lys Ala Leu Gly
  595                               600               605

Leu Pro Lys Tyr Thr Lys Leu Ile Thr Phe Asn Val His Asn Arg Tyr
  610                               615               620

Ala Ser Asn Ile Val Glu Ser Ala Tyr Leu Ile Leu Asn Glu Trp Lys
  625                               630               635               640

Asn Asn Ile Gln Ser Asp Leu Ile Lys Lys Val Thr Asn Tyr Leu Val
  645                               650               655

Asp Gly Asn Gly Arg Phe Val Phe Thr Asp Ile Thr Leu Pro Asn Ile
  660                               665               670

Ala Glu Gln Tyr Thr His Gln Asp Glu Ile Tyr Glu Gln Val His Ser
  675                               680               685

Lys Gly Leu Tyr Val Pro Glu Ser Arg Ser Ile Leu Leu His Gly Pro
  690                               695               700

Ser Lys Gly Val Glu Leu Arg Asn Asp Ser Glu Gly Phe Ile His Glu
  705                               710               715               720

Phe Gly His Ala Val Asp Asp Tyr Ala Gly Tyr Leu Leu Asp Lys Asn
  725                               730               735

Gln Ser Asp Leu Val Thr Asn Ser Lys Lys Phe Ile Asp Ile Phe Lys
  740                               745               750

Glu Glu Gly Ser Asn Leu Thr Ser Tyr Gly Arg Thr Asn Glu Ala Glu
  755                               760               765

Phe Phe Ala Glu Ala Phe Arg Leu Met His Ser Thr Asp His Ala Glu
  770                               775               780

Arg Leu Lys Val Gln Lys Asn Ala Pro Lys Thr Phe Gln Phe Ile Asn
  785                               790               795               800

Asp Gln Ile Lys Phe Ile Ile Asn Ser
  805

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<210> SEQ ID NO 6

<211> LENGTH: 23

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

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<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 6

caggtgcagc tgggtgcagtc tgg 23

<210> SEQ ID NO 7

<211> LENGTH: 23

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 7

caggtcaact taaggagtc tgg 23

<210> SEQ ID NO 8

<211> LENGTH: 23

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 8

gaggtgcagc tgggtggagtc tgg 23

<210> SEQ ID NO 9

<211> LENGTH: 23

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 9

caggtgcagc tgcaggagtc ggg 23

<210> SEQ ID NO 10

<211> LENGTH: 23

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 10

gaggtgcagc tgttgagtc tgc 23

<210> SEQ ID NO 11

<211> LENGTH: 23

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 11

caggtacagc tgcagcagtc agg 23

<210> SEQ ID NO 12

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL

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domains

<400> SEQUENCE: 12

tgaggagacg gtgaccaggg tgcc

24

<210> SEQ ID NO 13

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 13

tgaagagacg gtgaccattg tccc

24

<210> SEQ ID NO 14

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 14

tgaggagacg gtgaccaggg ttcc

24

<210> SEQ ID NO 15

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 15

tgaggagacg gtgaccgtgg tccc

24

<210> SEQ ID NO 16

<211> LENGTH: 23

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 16

gacatccaga tgaccagtc tcc

23

<210> SEQ ID NO 17

<211> LENGTH: 23

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 17

gatgttgtga tgactcagtc tcc

23

<210> SEQ ID NO 18

<211> LENGTH: 23

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

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<400> SEQUENCE: 18

gatattgtga tgactcagtc tcc

23

<210> SEQ ID NO 19

<211> LENGTH: 23

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 19

gaaattgtgt tgacgcagtc tcc

23

<210> SEQ ID NO 20

<211> LENGTH: 23

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 20

gacatcgtga tgaccacagtc tcc

23

<210> SEQ ID NO 21

<211> LENGTH: 23

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 21

gaaacgacac tcacgcagtc tcc

23

<210> SEQ ID NO 22

<211> LENGTH: 23

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 22

gaaattgtgc tgactcagtc tcc

23

<210> SEQ ID NO 23

<211> LENGTH: 23

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 23

cagtcgtgtg tgacgcagcc gcc

23

<210> SEQ ID NO 24

<211> LENGTH: 23

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

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<400> SEQUENCE: 24

cagtctgcc tgactcagcc tgc

23

<210> SEQ ID NO 25

<211> LENGTH: 23

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 25

tcctatgtgc tgactcagcc acc

23

<210> SEQ ID NO 26

<211> LENGTH: 23

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 26

tcttctgagc tgactcagga ccc

23

<210> SEQ ID NO 27

<211> LENGTH: 23

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 27

cacgttatac tgactcaacc gcc

23

<210> SEQ ID NO 28

<211> LENGTH: 23

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 28

caggctgtgc tcaactcagcc gtc

23

<210> SEQ ID NO 29

<211> LENGTH: 23

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 29

aattttatgc tgactcagcc cca

23

<210> SEQ ID NO 30

<211> LENGTH: 24

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 30

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acgtttgatt tccaccttgg tccc

24

<210> SEQ ID NO 31
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 31

acgtttgatc tccagcttgg tccc

24

<210> SEQ ID NO 32
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 32

acgtttgata tccactttgg tccc

24

<210> SEQ ID NO 33
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 33

acgtttgatc tccaccttgg tccc

24

<210> SEQ ID NO 34
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 34

acgtttaatc tccagtcgtg tccc

24

<210> SEQ ID NO 35
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 35

cagtcctgtgt tgacgcagcc gcc

23

<210> SEQ ID NO 36
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 36

-continued

cagtctgcc tgactcagcc tgc 23

<210> SEQ ID NO 37
 <211> LENGTH: 23
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 37

tcctatgtgc tgactcagcc acc 23

<210> SEQ ID NO 38
 <211> LENGTH: 23
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 38

tcttctgagc tgactcagga ccc 23

<210> SEQ ID NO 39
 <211> LENGTH: 23
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 39

cacgttatac tgactcaacc gcc 23

<210> SEQ ID NO 40
 <211> LENGTH: 23
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 40

caggctgtgc tcactcagcc gtc 23

<210> SEQ ID NO 41
 <211> LENGTH: 23
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: PCR primer useful for amplifying VH and VL domains

<400> SEQUENCE: 41

aattttatgc tgactcagcc cca 23

<210> SEQ ID NO 42
 <211> LENGTH: 489
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

Met Val Ala Glu Arg Ser Pro Ala Arg Ser Pro Gly Ser Trp Leu Phe
 1 5 10 15

Pro Gly Leu Trp Leu Leu Val Leu Ser Gly Pro Gly Gly Leu Leu Arg

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20							25				30				
Ala	Gln	Glu	Gln	Pro	Ser	Cys	Arg	Arg	Ala	Phe	Asp	Leu	Tyr	Phe	Val
35							40				45				
Leu	Asp	Lys	Ser	Gly	Ser	Val	Ala	Asn	Asn	Trp	Ile	Glu	Ile	Tyr	Asn
50							55				60				
Phe	Val	Gln	Gln	Leu	Ala	Glu	Arg	Phe	Val	Ser	Pro	Glu	Met	Arg	Leu
65							70				75				
Ser	Phe	Ile	Val	Phe	Ser	Ser	Gln	Ala	Thr	Ile	Ile	Leu	Pro	Leu	Thr
85							90				95				
Gly	Asp	Arg	Gly	Lys	Ile	Ser	Lys	Gly	Leu	Glu	Asp	Leu	Lys	Arg	Val
100							105				110				
Ser	Pro	Val	Gly	Glu	Thr	Tyr	Ile	His	Glu	Gly	Leu	Lys	Leu	Ala	Asn
115							120				125				
Glu	Gln	Ile	Gln	Lys	Ala	Gly	Gly	Leu	Lys	Thr	Ser	Ser	Ile	Ile	Ile
130							135				140				
Ala	Leu	Thr	Asp	Gly	Lys	Leu	Asp	Gly	Leu	Val	Pro	Ser	Tyr	Ala	Glu
145							150				155				
Lys	Glu	Ala	Lys	Ile	Ser	Arg	Ser	Leu	Gly	Ala	Ser	Val	Tyr	Cys	Val
165							170				175				
Gly	Val	Leu	Asp	Phe	Glu	Gln	Ala	Gln	Leu	Glu	Arg	Ile	Ala	Asp	Ser
180							185				190				
Lys	Glu	Gln	Val	Phe	Pro	Val	Lys	Gly	Gly	Phe	Gln	Ala	Leu	Lys	Gly
195							200				205				
Ile	Ile	Asn	Ser	Ile	Leu	Ala	Gln	Ser	Cys	Thr	Glu	Ile	Leu	Glu	Leu
210							215				220				
Gln	Pro	Ser	Ser	Val	Cys	Val	Gly	Glu	Glu	Phe	Gln	Ile	Val	Leu	Ser
225							230				235				
Gly	Arg	Gly	Phe	Met	Leu	Gly	Ser	Arg	Asn	Gly	Ser	Val	Leu	Cys	Thr
245							250				255				
Tyr	Thr	Val	Asn	Glu	Thr	Tyr	Thr	Thr	Ser	Val	Lys	Pro	Val	Ser	Val
260							265				270				
Gln	Leu	Asn	Ser	Met	Leu	Cys	Pro	Ala	Pro	Ile	Leu	Asn	Lys	Ala	Gly
275							280				285				
Glu	Thr	Leu	Asp	Val	Ser	Val	Ser	Phe	Asn	Gly	Gly	Lys	Ser	Val	Ile
290							295				300				
Ser	Gly	Ser	Leu	Ile	Val	Thr	Ala	Thr	Glu	Cys	Ser	Asn	Gly	Ile	Ala
305							310				315				
Ala	Ile	Ile	Val	Ile	Leu	Val	Leu	Leu	Leu	Leu	Gly	Ile	Gly	Leu	
325							330				335				
Met	Trp	Trp	Phe	Trp	Pro	Leu	Cys	Cys	Lys	Val	Val	Ile	Lys	Asp	Pro
340							345				350				
Pro	Pro	Pro	Pro	Pro	Pro	Ala	Pro	Lys	Glu	Glu	Glu	Glu	Glu	Pro	Leu
355							360				365				
Pro	Thr	Lys	Lys	Trp	Pro	Thr	Val	Asp	Ala	Ser	Tyr	Tyr	Gly	Gly	Arg
370							375				380				
Gly	Val	Gly	Gly	Ile	Lys	Arg	Met	Glu	Val	Arg	Trp	Gly	Asp	Lys	Gly
385							390				395				
Ser	Thr	Glu	Glu	Gly	Ala	Arg	Leu	Glu	Lys	Ala	Lys	Asn	Ala	Val	Val
405							410				415				
Lys	Ile	Pro	Glu	Glu	Thr	Glu	Glu	Pro	Ile	Arg	Pro	Arg	Pro	Pro	Arg
420							425				430				
Pro	Lys	Pro	Thr	His	Gln	Pro	Pro	Gln	Thr	Lys	Trp	Tyr	Thr	Pro	Ile
435							440				445				

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Lys Gly Arg Leu Asp Ala Leu Trp Ala Leu Leu Arg Arg Gln Tyr Asp
450 455 460

Arg Val Ser Leu Met Arg Pro Gln Glu Gly Asp Glu Val Cys Ile Trp
465 470 475 480

Glu Cys Ile Glu Lys Glu Leu Thr Ala
485

<210> SEQ ID NO 43
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: FLAG tag

<400> SEQUENCE: 43

Asp Tyr Lys Asp Asp Asp Asp Lys
1 5

<210> SEQ ID NO 44
<211> LENGTH: 137
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: human mature J chain

<400> SEQUENCE: 44

Gln Glu Asp Glu Arg Ile Val Leu Val Asp Asn Lys Cys Lys Cys Ala
1 5 10 15

Arg Ile Thr Ser Arg Ile Ile Arg Ser Ser Glu Asp Pro Asn Glu Asp
20 25 30

Ile Val Glu Arg Asn Ile Arg Ile Ile Val Pro Leu Asn Asn Arg Glu
35 40 45

Asn Ile Ser Asp Pro Thr Ser Pro Leu Arg Thr Arg Phe Val Tyr His
50 55 60

Leu Ser Asp Leu Cys Lys Lys Cys Asp Pro Thr Glu Val Glu Leu Asp
65 70 75 80

Asn Gln Ile Val Thr Ala Thr Gln Ser Asn Ile Cys Asp Glu Asp Ser
85 90 95

Ala Thr Glu Thr Cys Tyr Thr Tyr Asp Arg Asn Lys Cys Tyr Thr Ala
100 105 110

Val Val Pro Leu Val Tyr Gly Gly Glu Thr Lys Met Val Glu Thr Ala
115 120 125

Leu Thr Pro Asp Ala Cys Tyr Pro Asp
130 135

<210> SEQ ID NO 45
<211> LENGTH: 137
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Mutant form of human mature J chain with C134S
mutation compared to wild type Mature form of human J chain (SEQ
ID NO:44)

<400> SEQUENCE: 45

Gln Glu Asp Glu Arg Ile Val Leu Val Asp Asn Lys Cys Lys Cys Ala
1 5 10 15

Arg Ile Thr Ser Arg Ile Ile Arg Ser Ser Glu Asp Pro Asn Glu Asp
20 25 30

Ile Val Glu Arg Asn Ile Arg Ile Ile Val Pro Leu Asn Asn Arg Glu

-continued

35	40	45
Asn Ile Ser Asp Pro Thr	Ser Pro Leu Arg Thr	Arg Phe Val Tyr His
50	55	60
Leu Ser Asp Leu Cys Lys	Lys Cys Asp Pro Thr	Glu Val Glu Leu Asp
65	70	75 80
Asn Gln Ile Val Thr Ala	Thr Gln Ser Asn Ile	Cys Asp Glu Asp Ser
85	90	95
Ala Thr Glu Thr Cys Tyr	Thr Tyr Asp Arg Asn	Lys Cys Tyr Thr Ala
100	105	110
Val Val Pro Leu Val Tyr	Gly Gly Glu Thr Lys	Met Val Glu Thr Ala
115	120	125
Leu Thr Pro Asp Ala Ser	Tyr Pro Asp	
130	135	

<210> SEQ ID NO 46

<211> LENGTH: 112

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Mutant form of human mature J chain with amino acids 113-137 deleted compared to wild type Mature form of human J chain (SEQ ID NO:44)

<400> SEQUENCE: 46

Gln Glu Asp Glu Arg Ile	Val Leu Val Asp Asn	Lys Cys Lys Cys Ala
1	5	10 15
Arg Ile Thr Ser Arg Ile	Ile Arg Ser Ser Glu	Asp Pro Asn Glu Asp
20	25	30
Ile Val Glu Arg Asn Ile	Arg Ile Ile Val Pro	Leu Asn Asn Arg Glu
35	40	45
Asn Ile Ser Asp Pro Thr	Ser Pro Leu Arg Thr	Arg Phe Val Tyr His
50	55	60
Leu Ser Asp Leu Cys Lys	Lys Cys Asp Pro Thr	Glu Val Glu Leu Asp
65	70	75 80
Asn Gln Ile Val Thr Ala	Thr Gln Ser Asn Ile	Cys Asp Glu Asp Ser
85	90	95
Ala Thr Glu Thr Cys Tyr	Thr Tyr Asp Arg Asn	Lys Cys Tyr Thr Ala
100	105	110

<210> SEQ ID NO 47

<211> LENGTH: 137

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Mutant form of human mature J chain with C109S and C134S mutation compared to wild type mature form of human J chain (SEQ ID NO:44)

<400> SEQUENCE: 47

Gln Glu Asp Glu Arg Ile	Val Leu Val Asp Asn	Lys Cys Lys Cys Ala
1	5	10 15
Arg Ile Thr Ser Arg Ile	Ile Arg Ser Ser Glu	Asp Pro Asn Glu Asp
20	25	30
Ile Val Glu Arg Asn Ile	Arg Ile Ile Val Pro	Leu Asn Asn Arg Glu
35	40	45
Asn Ile Ser Asp Pro Thr	Ser Pro Leu Arg Thr	Arg Phe Val Tyr His
50	55	60
Leu Ser Asp Leu Cys Lys	Lys Cys Asp Pro Thr	Glu Val Glu Leu Asp
65	70	75 80

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Asn Gln Ile Val Thr Ala Thr Gln Ser Asn Ile Cys Asp Glu Asp Ser
85 90 95

Ala Thr Glu Thr Cys Tyr Thr Tyr Asp Arg Asn Lys Ser Tyr Thr Ala
100 105 110

Val Val Pro Leu Val Tyr Gly Gly Glu Thr Lys Met Val Glu Thr Ala
115 120 125

Leu Thr Pro Asp Ala Ser Tyr Pro Asp
130 135

<210> SEQ ID NO 48
<211> LENGTH: 248
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: PWB2447 scFv

<400> SEQUENCE: 48

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Ser Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ser Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Val Ser Tyr Asp Gly Ser Asn Ile Tyr Tyr Ile Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Ala Lys Ala Gly Arg Arg Thr Gln Leu Gln Pro Arg Asp Phe Leu Phe
100 105 110

Glu Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Glu Leu Thr
130 135 140

Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile Thr
145 150 155 160

Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln Gln
165 170 175

Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr Gly Lys Asn Asn Arg
180 185 190

Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn Thr
195 200 205

Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp Tyr
210 215 220

Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn His Val Val Phe Gly Gly
225 230 235 240

Gly Thr Lys Leu Thr Val Leu Gly
245

<210> SEQ ID NO 49
<211> LENGTH: 251
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: PWC2004 scFv

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<400> SEQUENCE: 49

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Arg Lys Pro Gly Ala
 1 5 10 15
 Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Met Phe Thr Gly Tyr
 20 25 30
 Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
 35 40 45
 Gly Trp Ile Lys Pro Tyr Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
 50 55 60
 His Asp Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
 65 70 75 80
 Met Glu Val Met Arg Leu Thr Ser Asp Asp Ser Ala Val Phe Tyr Cys
 85 90 95
 Ala Arg Ser Arg Tyr Ser Ser Ser Pro Phe Arg Gly Gly Leu Asp Val
 100 105 110
 Trp Gly Arg Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly Gly Ser
 115 120 125
 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Gln Ala Val Leu Thr
 130 135 140
 Gln Pro Ser Ser Val Ser Gly Ala Pro Gly Gln Arg Val Thr Ile Ser
 145 150 155 160
 Cys Thr Gly Ser Ser Ser Asn Ile Gly Asp Gly Tyr Asp Val His Trp
 165 170 175
 Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Gly Asn
 180 185 190
 Thr Asn Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser
 195 200 205
 Asp Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln Val Glu Asp Glu
 210 215 220
 Ala Asp Tyr Phe Cys His Ser Tyr Asp Ser Ser Ile Ser Gly Trp Ile
 225 230 235 240
 Phe Gly Gly Gly Thr Lys Val Thr Val Leu Gly
 245 250

<210> SEQ ID NO 50

<211> LENGTH: 246

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: PWD0283 scFv

<400> SEQUENCE: 50

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ala Thr Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Val Gly Gly Ala Ile Arg Phe Asp Ser Trp Gly Arg Gly Thr

-continued

100	105	110
Leu Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly Gly Ser		
115	120	125
Gly Gly Gly Gly Ser Ala Leu Ser Tyr Glu Leu Thr Gln Pro Pro Ser		
130	135	140
Ala Ser Glu Thr Pro Gly Gln Arg Val Ser Ile Ser Cys Ser Gly Gly		
145	150	155
Thr Ser Asn Ile Gly Ser Asn Thr Ile Asn Trp Tyr Gln Gln Val Pro		
165	170	175
Gly Thr Ala Pro Lys Leu Leu Ile Tyr Phe Asn Asn Arg Arg Pro Ala		
180	185	190
Gly Val Pro Ala Arg Phe Ser Ala Ser Lys Ser Gly Thr Ser Ala Ser		
195	200	205
Leu Thr Ile Ser Gly Leu Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys		
210	215	220
Ser Ala Trp Asp Asp Ser Leu Ser Gly Val Val Phe Gly Gly Gly Thr		
225	230	235
Lys Leu Thr Val Leu Gly		
245		

<210> SEQ ID NO 51
 <211> LENGTH: 244
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: PWD0323 scFv

<400> SEQUENCE: 51

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly		
1	5	10
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr		
20	25	30
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val		
35	40	45
Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val		
50	55	60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr		
65	70	75
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys		
85	90	95
Ala Arg Gln Ile Trp Gly Arg Phe Glu Tyr Trp Gly Arg Gly Thr Thr		
100	105	110
Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly		
115	120	125
Gly Gly Gly Ser Ala Gln Ala Val Leu Thr Gln Pro Ser Ser Ala Ser		
130	135	140
Gly Thr Pro Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser		
145	150	155
Asn Ile Gly Thr Asn Thr Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr		
165	170	175
Ala Pro Lys Leu Leu Ile Phe Ser Asn Asn Gln Arg Pro Ser Gly Val		
180	185	190
Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Pro Ser Ala Ser Leu Ala		
195	200	205
Ile Ser Gly Leu Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala		

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210	215	220
Trp Asp Asp Arg Leu Asn Gly Tyr Val Phe	Gly Thr Gly Thr Lys Leu	
225	230	235 240

Thr Val Leu Gly

<210> SEQ ID NO 52
 <211> LENGTH: 244
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: PWD0422 scFv

<400> SEQUENCE: 52

Glu Val Gln Leu Leu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Gln Ala Phe Ala Arg Phe Glu Phe Trp Gly Arg Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Ala Gln Ser Val Val Thr Gln Pro Pro Ser Val Ser
130 135 140

Gly Thr Pro Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser
145 150 155 160

Asn Ile Gly Thr Asn Thr Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr
165 170 175

Ala Pro Lys Leu Leu Ile Tyr Ser Asn Asn Gln Arg Pro Ser Gly Val
180 185 190

Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Val Ala
195 200 205

Ile Ser Gly Leu Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser
210 215 220

Trp Asp Asp Ser Leu Asn Gly Val Val Phe Gly Gly Gly Thr Lys Leu
225 230 235 240

Thr Val Leu Gly

<210> SEQ ID NO 53
 <211> LENGTH: 244
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: PWD0587 scFv

<400> SEQUENCE: 53

Glu Val Gln Leu Leu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

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Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Gln Ile Trp Gly Arg Phe Glu Tyr Trp Gly Arg Gly Thr Thr
 100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
 115 120 125

Gly Gly Gly Ser Ala Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser
 130 135 140

Gly Thr Pro Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser
 145 150 155 160

Asn Ile Gly Ser Asn Thr Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr
 165 170 175

Ala Pro Lys Leu Leu Ile Tyr Ser Asn Asn Gln Arg Pro Ser Gly Val
 180 185 190

Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala
 195 200 205

Ile Ser Gly Leu Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala
 210 215 220

Trp Asp Asp Ser Leu Asn Gly Val Val Phe Gly Gly Gly Thr Lys Leu
 225 230 235 240

Thr Val Leu Gly

<210> SEQ ID NO 54
 <211> LENGTH: 248
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: PWD0791 scFv

<400> SEQUENCE: 54

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Leu Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ile Ser Tyr
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Val Asp His Lys Trp Asp Leu Pro Phe Asp Tyr Trp Gly Arg
 100 105 110

Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly
 115 120 125

Gly Ser Gly Gly Gly Gly Ser Ala Leu Ser Tyr Val Leu Thr Gln Pro
 130 135 140

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Pro Ser Ala Ser Gly Thr Pro Gly Gln Arg Val Val Val Ser Cys Ser
 145 150 155 160

Gly Gly Ser Ser Asn Ile Gly Lys Asn Pro Val Thr Trp Tyr Gln His
 165 170 175

Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Ser Arg Asn Thr Gln Arg
 180 185 190

Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser
 195 200 205

Ala Ser Leu Ala Ile Ser Gly Leu Gln Ser Glu Asp Glu Ala Asp Tyr
 210 215 220

Tyr Cys Ala Ala Trp Asp Asp Ser Leu Lys Gly Trp Val Phe Gly Gly
 225 230 235 240

Gly Thr Lys Leu Thr Val Leu Gly
 245

<210> SEQ ID NO 55
 <211> LENGTH: 244
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: PHD2222 scFv

<400> SEQUENCE: 55

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Arg Gln Ile Trp Gly Arg Phe Glu Tyr Trp Gly Arg Gly Thr Thr
 100 105 110

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly
 115 120 125

Gly Gly Gly Ser Ala Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser
 130 135 140

Gly Thr Pro Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser
 145 150 155 160

Asn Ile Gly Ser Asn Thr Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr
 165 170 175

Ala Pro Lys Leu Leu Ile Tyr Ser Asn Asn Gln Arg Pro Ser Gly Val
 180 185 190

Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala
 195 200 205

Val Ser Gly Leu Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala
 210 215 220

Trp Asp Asp Ser Leu Asn Gly Val Val Phe Gly Gly Gly Thr Lys Leu
 225 230 235 240

Thr Val Leu Gly

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<210> SEQ ID NO 56
 <211> LENGTH: 244
 <212> TYPE: PRT
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: PHD2581 scFv

<400> SEQUENCE: 56

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Arg Gln Ile Trp Gly Arg Phe Glu Tyr Trp Gly Lys Gly Thr Met
 100 105 110
 Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly
 115 120 125
 Gly Gly Gly Ser Ala Gln Ser Val Leu Thr Gln Pro Ser Ala Ser
 130 135 140
 Gly Thr Pro Gly Gln Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser
 145 150 155 160
 Asn Ile Gly Ser Asn Thr Val Asn Trp Tyr Gln Gln Leu Pro Gly Thr
 165 170 175
 Ala Pro Lys Leu Leu Ile Tyr Ser Asn Asn Gln Arg Pro Ser Gly Val
 180 185 190
 Pro Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala
 195 200 205
 Ile Ser Gly Leu Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala
 210 215 220
 Trp Asp Asp Ser Leu Asn Gly Val Val Phe Gly Gly Gly Thr Lys Leu
 225 230 235 240
 Thr Val Leu Gly

<210> SEQ ID NO 57
 <211> LENGTH: 744
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: DNA encoding PWB2447 scFv

<400> SEQUENCE: 57

cagggtgcagc tgggtggagtc tgggggaggc gtggtccagt ctgggggggc cctgaggctc 60
 tcctgttcag cgctctgatt caccctcagt gactatggca tgcaactggg cgcacaggct 120
 ccaggcaagg ggctggagtg ggtggcagtc gtgtcatatg atggaagtaa tatatactat 180
 atagactccg tgaagggccg ttccaccatc tccagagacg attccaagaa cacgctttat 240
 ctccaaatga acagcctgag agctgaggac acggctctgt attactgtgc gaaagctggg 300
 aggcgaaccc aattacaacc cagagacttt ctttttgagt actggggcca aggaaccctg 360
 gtcaccgtct cgagtgggtgg aggcggttca ggcggagggt gcagcggcgg tggcggatcg 420

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tctgagctga ctcaggaccc tgctgtgtct gtggccttgg gacagacagt caggatcaca	480
tgccaaggag acagcctcag aagctattat gcaagctggt accagcagaa gccaggacag	540
gccccgttac ttgtcatcta cggtaaaaac aaccggccct cagggatccc agaccgattc	600
tctggctcca gctcaggaaa cacagcttcc ttgaccatca ctggggctca ggcggaagat	660
gaggctgact attactgtaa ctcccgggac agcagtggta accatgtggt attcggcgga	720
gggaccaagc tgaccgtcct aggt	744

<210> SEQ ID NO 58
 <211> LENGTH: 753
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: DNA encoding PWC2004 scFv

<400> SEQUENCE: 58

cagggtccagc tgggtgcagtc tggggctgag gtgaggaagc ctggggcctc agtgaaggtc	60
tcctgcaagg ctctcgata catgttcacc ggctactata tgcactgggt gcgacaggcc	120
cctggacaag ggcttgagtg gatgggatgg atcaagcctt acagtgggtg cacaactat	180
gcacagaagt ttcacgacag ggtcacccatg accagggaca cgtccatcag cacagcctac	240
atggagggtga tgaggctgac atctgacgac agcgcctgtt tttactgtgc gagaagccgc	300
tatagcagca gcccttttag ggggggtttg gacgtctggg gccgagggac aatggtcacc	360
gtctcgagtg gaggcgccgg ttcaggcgga ggtggctctg gcggtggcgg aagtgcacag	420
gctgtgtga ctcagccgtc ctcagtgtct ggggccccag ggcagagggt caccatctcc	480
tgcactggga gcagctccaa catcggggac ggttatgatg tccactggta tcagcaactt	540
ccaggaacag cccccaaact cctcatctat ggtaacacta atcgccctc aggggtccct	600
gaccgattct ctggctccaa gtctgacacc tctgctccc tggccatcac tgggtccag	660
gttgaggatg aggtcgatta tttctgccac tcctatgaca gcagtatcag tggctggatt	720
ttcggcggag ggaccaaggt caccgtccta ggt	753

<210> SEQ ID NO 59
 <211> LENGTH: 738
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: DNA encoding PWD0283 scFv

<400> SEQUENCE: 59

gagggtgcagc tgttgagtc tgggggagggc ttggtacagc ctgggggggtc cctgagactc	60
tcctgtgcag cctctggatt cacccttagc agctatgcca cgagctgggt ccgccaggct	120
ccagggaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactac	180
gcagactccg tgaaggggcg gttcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gagagtgggg	300
ggagccattc gctttgactc ctggggcagg ggaaccctgg tcaccgtctc gagtggagge	360
ggcgggttcag gcggagggtg ctctggcggg ggcggaagtg cactttccta tgagctgact	420
cagccaccct cagcgtctga gacccccggg cagagggtct ccatctcttg ttctggaggc	480
acctcgaaca tcggatccaa cactatcaac tgggtaccagc aggtcccagg aacggcccc	540
aaactactca tctattttta taatcggcgg cccgcagggg tccctgcccc attttctgac	600

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tccaagtctg gcacctcagc ctccttgacc atcagtgggc tccagtctga ggatgaggct	660
gactattatt gttcagcatg ggatgacagc ctgagtggcg tgggtgttcgg cggaggggacc	720
aagctgaccg tccataggt	738

<210> SEQ ID NO 60
 <211> LENGTH: 732
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: DNA encoding PWD0323 scFv

<400> SEQUENCE: 60

gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctggggggtc cctgagactc	60
tcctgtgcag cctctggatt caccttttagc agctatgccca tgagctgggt ccgccaggct	120
ccaggggaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactac	180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gaggcaaatc	300
tggggacgat ttgaatatgg ggggaggggg accacggtca ccgtctcgag tggaggcggc	360
ggttcaggcg gaggtggctc tggcgggtggc ggaagtgcac aggctgtgct gactcagccg	420
tcctcagcgt ctggggacccc cgggcagagg gtcaccatct cttgttctgg aagcagctcc	480
aacatcgga ctaatactgt aaactggtag caacagctcc caggaaacggc ccccaaaactc	540
ctcatcttta gtaataatca acggccctca ggggtccctg accgattctc tggctccaag	600
tctggcccct cagcctccct ggccatcagt ggactccagt ccgaggatga ggctgattat	660
tactgtgcag catgggatga caggctgaat ggttatgtct tcggaactgg gaccaagctg	720
accgtcctag gt	732

<210> SEQ ID NO 61
 <211> LENGTH: 732
 <212> TYPE: DNA
 <213> ORGANISM: Artificial sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: DNA encoding PWD0422 scFv

<400> SEQUENCE: 61

gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctggggggtc cctgagactc	60
tcctgtgcag cctctggatt caccttttagc agctatgccca tgagctgggt ccgccaggct	120
ccaggggaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactac	180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gaccagggcc	300
tttgcctggt tcgagttttg gggccggggc accctgggtca ccgtctcgag tggaggcggc	360
ggttcaggcg gaggtggctc tggcgggtggc ggaagtgcac agtctgtcgt gacgcagccg	420
ccctcagtggt ctgggacccc cgggcagagg gtcaccatct cttgttctgg aagcagctcc	480
aacatcgga ctaatactgt aaactggtag caacaactcc caggaaacggc ccccaaaactc	540
ctcatctata gtaataatca gcgacccctca ggggtccctg accgattctc tggctccaag	600
tctggcacct cagcctccgt ggccatcagt gggctccagt ctgaggatga ggctgattac	660
tactgttctt catgggatga cagcctgaat ggcgtcgtgt tcggcggagg gaccaagctg	720
accgtcctag gt	732

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<210> SEQ ID NO 62
<211> LENGTH: 732
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: DNA encoding PWD0587 scFv

<400> SEQUENCE: 62
gaggtgcagc tgttggagtc tgggggaggc ttggtacagc ctggggggtc cctgagactc   60
tcctgtgcag cctctggatt cacctttagc agctatgcc a tgagctgggt ccgccaggct   120
ccaggggaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactac   180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat   240
ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gaggcaaata   300
tggggacgat ttgaatattg ggggcggggg accacggtea ccgtctcgag tggaggcggc   360
gggttcaggcg gaggtggctc tggcgtggc ggaagtgcac agtctgtgct gactcagcca   420
ccctcagcgt ctgggacccc cgggcagagg gtcaccatct cttgttctgg aagcagctcc   480
aacatcgga gtaataatgt aaactggtac cagcagctcc caggaacggc ccccaaaactc   540
ctcatctata gtaataatca gcggccctca ggggtccctg accgattctc tggctccaag   600
tctggcacct cagcctccct ggccatcagt gggctccagt ctgaggatga ggctgattat   660
tactgtgcag catgggatga cagcctgaat ggagtggat tcggcggagg gaccaagctg   720
accgtcctag gt                                     732

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<210> SEQ ID NO 63
<211> LENGTH: 744
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: DNA encoding PWD0791 scFv

<400> SEQUENCE: 63
gaggtgcagc tgttggagtc tgggggaggc ttgttacagc ctggggggtc cctgagactc   60
tcctgtgcag cctctggatt ctcttttacc agctatgcc a tgagctgggt ccgccaggct   120
ccaggggaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactac   180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat   240
ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc cagagtggac   300
cataaatggg acctaccctt tgactactgg ggccgaggca ccctgggtcac cgtctcgagt   360
ggaggcggcg gttcaggcgg aggtggctct ggcggtgggc gaagtgcact ttcctatgtg   420
ctgactcagc caccctcagc gtctggaacc cccgggcaga gggctcgtct ctcttgttct   480
gggggcagct ccaacatcgg aaaaaatcct gtaacctggt atcagcacct cccaggaacg   540
gcccccaaac tctcatctc tagaaatact cagcggccct caggagtccc tgaccgatcc   600
tctggctcca agtctggcac gtcagcctcc ctggccatca gtgggctcca gtctgaggat   660
gaggctgatt attactgtgc agcatgggat gacagcctca agggctgggt gttcggcgga   720
gggaccaagc tgaccgtctc aggt                                     744

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<210> SEQ ID NO 64
<211> LENGTH: 732
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: DNA encoding PHD2222 scFv

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<400> SEQUENCE: 64

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gagggtgcagc tgttggagtc tgggggagggc ttggtacagc ctgggggggc cctgagactc   60
tctgtgcag cctctggatt cacctttagc agctatgcc a tgagctgggt ccgccaggct   120
ccaggggaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactac   180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat   240
ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gaggcaaatc   300
tggggacgct ttgaatattg gggggcgggg accacggcca ccgtctcgag tggaggcggc   360
gggtcaggcg gagggtggctc tggcggtggc ggaagtgcac agtctgtgct gactcagcca   420
ccctcagcgt ctgggacccc cgggcagagg gtcaccatct cttgttctgg aagcagctcc   480
aacatcgga gtaataactgt aaactggtag cagcagctcc caggaacggc ccccaaaactc   540
ctcatctata gtaataatca gcggccctca ggggtccctg accgattctc tggctccaag   600
tctggcacct cagcctccct ggccgtcagt gggctccagt ctgaggatga ggctgattat   660
tactgtgcag catgggatga cagcctgaat ggtgtggtat tcggcggagg gaccaagctg   720
accgtcctag gt                                     732

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<210> SEQ ID NO 65

<211> LENGTH: 732

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: DNA encoding PHD2581 sequence

<400> SEQUENCE: 65

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gagggtgcagc tgttggagtc tgggggagggc ttggtacagc ctgggggggc cctgagactc   60
tctgtgcag cctctggatt cacctttagc agctatgcc a tgagctgggt ccgccaggct   120
ccaggggaagg ggctggagtg ggtctcagct attagtggta gtggtggtag cacatactac   180
gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgtat   240
ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gaggcaaatc   300
tggggacgat ttgaatattg gggcaaaagg acaatggtag ccgtctcgag tggaggcggc   360
gggtcaggcg gagggtggctc tggcggtggc ggaagtgcac agtctgtgct gactcagcca   420
ccctcagcgt ctgggacccc cgggcagagg gtcaccatct cttgttctgg aagcagctcc   480
aacatcgga gtaataactgt aaactggtag cagcagctcc caggaacggc ccccaaaactc   540
ctcatctata gtaataatca gcggccctca ggggtccctg accgattctc tggctccaag   600
tctggcacct cagcctccct ggccatcagt gggctccagt ctgaggatga ggctgattat   660
tactgtgcgg catgggatga cagcctgaat ggtgtggtat tcggcggagg gaccaagctg   720
accgtcctag gt                                     732

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<210> SEQ ID NO 66

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 66

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His Ser Pro Gly Asp Tyr Ala Phe Asp Tyr
1         5         10

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<210> SEQ ID NO 67

<211> LENGTH: 10

<212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 67

His Ser Pro Gly Asp Tyr Ala Phe Asp Tyr
1 5 10

<210> SEQ ID NO 68

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 68

His Ser Pro Gly Asp Tyr Ala Phe Asp Tyr
1 5 10

<210> SEQ ID NO 69

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 69

Ala Gly Arg Arg Thr Gln Leu Gln Pro Arg Asp Phe Leu Phe Glu Tyr
1 5 10 15

<210> SEQ ID NO 70

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 70

Ala Gly Arg Arg Thr Gln Leu Gln Pro Arg Asp Phe Leu Phe Glu Tyr
1 5 10 15

<210> SEQ ID NO 71

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 71

Ala Gly Arg Arg Thr Gln Leu Gln Pro Arg Asp Phe Leu Phe Glu Tyr
1 5 10 15

<210> SEQ ID NO 72

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 72

Ala Gly Arg Arg Thr Gln Leu Gln Pro Arg Asp Phe Leu Phe Glu Tyr
1 5 10 15

<210> SEQ ID NO 73

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 73

Ala Gly Arg Arg Thr Gln Leu Gln Pro Arg Asp Phe Leu Phe Glu Tyr
1 5 10 15

<210> SEQ ID NO 74

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 74

His Ser Pro Gly Asp Tyr Ala Phe Asp Tyr
1 5 10

<210> SEQ ID NO 75

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 75

His Ser Pro Gly Asp Tyr Ala Phe Asp Tyr
1 5 10

<210> SEQ ID NO 76

<211> LENGTH: 12

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 76

Ala Ser Tyr Leu Ser Thr Ser Ser Ser Leu Asp Tyr
1 5 10

<210> SEQ ID NO 77

<211> LENGTH: 12

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 77

Ala Ser Tyr Leu Ser Thr Ser Ser Ser Leu Asp Tyr
1 5 10

<210> SEQ ID NO 78

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 78

Ala Gly Arg Arg Thr Gln Leu Gln Pro Arg Asp Phe Leu Phe Glu Tyr
1 5 10 15

<210> SEQ ID NO 79

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 79

Asp Leu Asp Ser Ser Thr Ile Pro His Arg Glu Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 80

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 80

Ala Gly Arg Arg Thr Gln Leu Gln Pro Arg Asp Phe Leu Phe Glu Tyr
1 5 10 15

<210> SEQ ID NO 81

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 81

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Ala Gly Arg Arg Thr Gln Leu Gln Pro Arg Asp Phe Leu Phe Glu Tyr
1 5 10 15

<210> SEQ ID NO 82
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 82

Ala Gly Arg Arg Thr Gln Leu Gln Pro Arg Asp Phe Leu Phe Glu Tyr
1 5 10 15

<210> SEQ ID NO 83
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 83

Ala Ser Asn Leu Ser Thr Ser Ser Leu Asp Tyr.
1 5 10

<210> SEQ ID NO 84
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 84

Ser Gly Ser Ser Trp Ser His Phe Asp Phe
1 5 10

<210> SEQ ID NO 85
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 85

Gly Ser Pro Thr Gly Asp Leu Asn Val Asp Val Phe Asp Tyr
1 5 10

<210> SEQ ID NO 86
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 86

His Ser Pro Gly Asp Tyr Ala Phe Asp Tyr
1 5 10

<210> SEQ ID NO 87
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 87

Val Arg Asp Ile Arg Pro Gly Asp Tyr Ala Phe Asp Tyr
1 5 10

<210> SEQ ID NO 88
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 88

Ala Gly Arg Arg Thr Gln Leu Gln Pro Arg Asp Phe Leu Phe Glu Tyr
1 5 10 15

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<210> SEQ ID NO 89
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 89

His Ser Pro Gly Asp Tyr Ala Phe Asp Tyr
1 5 10

<210> SEQ ID NO 90
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 90

Ala Ser Tyr Leu Ser Thr Ser Pro Ser Leu Asp Tyr
1 5 10

<210> SEQ ID NO 91
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 91

Ala Gly Arg Arg Thr Gln Leu Gln Pro Arg Asp Phe Leu Phe Glu Tyr
1 5 10 15

<210> SEQ ID NO 92
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 92

His Ser Pro Gly Asp Tyr Ala Phe Asp Tyr
1 5 10

<210> SEQ ID NO 93
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 93

Ala Gly Arg Arg Thr Gln Leu Gln Pro Arg Asp Phe Leu Phe Glu Tyr
1 5 10 15

<210> SEQ ID NO 94
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 94

Ser Gly Ser Ser Trp Ser His Phe Asp Phe
1 5 10

<210> SEQ ID NO 95
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 95

Ala Gly Arg Arg Thr Gln Leu Pro Pro Arg Asp Phe Leu Phe Glu His
1 5 10 15

-continued

<210> SEQ ID NO 96
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 96

His Ser Pro Gly Asp Tyr Ala Phe Asp Tyr
1 5 10

<210> SEQ ID NO 97
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 97

Ala Ser Asn Leu Ser Thr Ser Pro Ser Leu Asp Tyr
1 5 10

<210> SEQ ID NO 98
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 98

Ala Gly Arg Arg Thr Gln Leu Gln Pro Ile Asp Phe Leu Phe Glu Tyr
1 5 10 15

<210> SEQ ID NO 99
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 99

Ala Gly Arg Arg Thr Gln Leu Gln Pro Arg Asp Phe Leu Phe Glu Tyr
1 5 10 15

<210> SEQ ID NO 100
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 100

His Ser Pro Gly Asp Tyr Ala Phe Asp Tyr
1 5 10

<210> SEQ ID NO 101
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 101

Ala Gly Arg Arg Thr Gln Leu Gln Pro Arg Asp Phe Leu Phe Glu Tyr
1 5 10 15

<210> SEQ ID NO 102
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 102

Gly Ser Gly Tyr Ser Gly Tyr Asp Phe Pro Tyr Tyr Tyr Gly Met Asp
1 5 10 15

Val

-continued

<210> SEQ ID NO 103
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 103

Ala Gly Arg Arg Thr Gln Leu Gln Pro Arg Asp Phe Leu Phe Glu Tyr
1 5 10 15

<210> SEQ ID NO 104
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 104

Ala Gly Arg Arg Thr Gln Leu Gln Pro Arg Asp Phe Leu Phe Glu Tyr
1 5 10 15

<210> SEQ ID NO 105
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 105

Ala Gly Arg Arg Thr Gln Leu Gln Pro Arg Asp Phe Leu Phe Glu Tyr
1 5 10 15

<210> SEQ ID NO 106
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 106

Ala Gly Arg Arg Thr Gln Leu Gln Pro Arg Asp Phe Leu Phe Glu Tyr
1 5 10 15

<210> SEQ ID NO 107
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 107

Asp Ser Ser Ser Gly Trp Phe Phe Ile Asp Tyr
1 5 10

<210> SEQ ID NO 108
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 108

Ala Arg Asp Ser Ser Ser Gly Trp Phe Phe Ile Asp Tyr
1 5 10

<210> SEQ ID NO 109
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 109

Asp Ser Ser Ser Gly Trp Phe Phe Ile Asp Tyr
1 5 10

<210> SEQ ID NO 110
<211> LENGTH: 11

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 110

Asp Ser Ser Ser Gly Trp Phe Phe Ile Asp Tyr
1 5 10

<210> SEQ ID NO 111
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 111

Asp Ser Ser Ser Gly Trp Phe Phe Ile Asp Tyr
1 5 10

<210> SEQ ID NO 112
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 112

Asp Ser Ser Ser Gly Trp Phe Phe Ile Asp Tyr
1 5 10

<210> SEQ ID NO 113
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 113

Asp Ser Ser Ser Gly Trp Phe Phe Ile Asp Tyr
1 5 10

<210> SEQ ID NO 114
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 114

Asp Ser Ser Ser Gly Trp Phe Phe Ile Asp Tyr
1 5 10

<210> SEQ ID NO 115
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 115

Asp Ser Ser Ser Gly Trp Phe Phe Ile Asp Tyr
1 5 10

<210> SEQ ID NO 116
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 116

Asp Ser Ser Ser Gly Trp Phe Phe Ile Asp Tyr
1 5 10

<210> SEQ ID NO 117
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 117

Asp Ser Ser Ser Gly Trp Phe Phe Ile Asp Tyr
1 5 10

<210> SEQ ID NO 118

<211> LENGTH: 14

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 118

Ser Arg Tyr Ser Ser Ser Pro Phe Arg Gly Gly Leu Asp Val
1 5 10

<210> SEQ ID NO 119

<211> LENGTH: 14

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 119

Ser Arg Tyr Ser Ser Ser Pro Phe Arg Gly Gly Leu Asp Val
1 5 10

<210> SEQ ID NO 120

<211> LENGTH: 14

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 120

Ser Arg Tyr Ser Ser Ser Pro Phe Arg Gly Gly Leu Asp Val
1 5 10

<210> SEQ ID NO 121

<211> LENGTH: 14

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 121

Ser Arg Tyr Ser Ser Ser Pro Phe Arg Gly Gly Leu Asp Val
1 5 10

<210> SEQ ID NO 122

<211> LENGTH: 14

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 122

Ser Arg Tyr Ser Ser Ser Pro Phe Arg Gly Gly Leu Asp Val
1 5 10

<210> SEQ ID NO 123

<211> LENGTH: 14

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 123

Ser Arg Tyr Ser Ser Ser Pro Phe Arg Gly Gly Leu Asp Val
1 5 10

<210> SEQ ID NO 124

<211> LENGTH: 14

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 124

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Ser Arg Tyr Ser Ser Ser Pro Phe Arg Gly Gly Leu Asp Val
1 5 10

<210> SEQ ID NO 125
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 125

Ser Arg Tyr Ser Ser Ser Pro Phe Arg Gly Gly Leu Asp Val
1 5 10

<210> SEQ ID NO 126
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 126

Ser Arg Tyr Ser Ser Ser Pro Phe Arg Gly Gly Leu Asp Val
1 5 10

<210> SEQ ID NO 127
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 127

Ser Arg Tyr Ser Ser Ser Pro Phe Arg Gly Gly Leu Asp Val
1 5 10

<210> SEQ ID NO 128
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 128

Ser Ser Ser Gly Cys Leu Phe Ile Asp Tyr
1 5 10

<210> SEQ ID NO 129
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 129

Ser Arg Tyr Ser Ser Ser Pro Phe Arg Gly Gly Leu Asp Val
1 5 10

<210> SEQ ID NO 130
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 130

Ser Arg Tyr Ser Ser Ser Pro Phe Arg Gly Gly Leu Asp Val
1 5 10

<210> SEQ ID NO 131
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 131

Asp Ser Ser Ser Gly Trp Phe Phe Ile Asp Tyr

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<210> SEQ ID NO 132
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 132

Ser Arg Tyr Ser Ser Ser Pro Phe Arg Gly Gly Leu Asp Val
1 5 10

<210> SEQ ID NO 133
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 133

Ser Arg Tyr Ser Ser Ser Pro Phe Arg Gly Gly Leu Asp Val
1 5 10

<210> SEQ ID NO 134
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 134

Ser Arg Tyr Ser Ser Ser Pro Phe Arg Gly Gly Leu Asp Val
1 5 10

<210> SEQ ID NO 135
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 135

Asp Ser Ser Ser Gly Trp Phe Phe Ile
1 5

<210> SEQ ID NO 136
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 136

Ser Ser Ser Gly Trp Leu Phe Ile Asp Tyr
1 5 10

<210> SEQ ID NO 137
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 137

Ser Arg Tyr Ser Ser Ser Pro Phe Arg Gly Gly Leu Asp Val
1 5 10

<210> SEQ ID NO 138
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 138

Ser Arg Tyr Ser Ser Ser Pro Phe Arg Gly Gly Leu Asp Val
1 5 10

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<210> SEQ ID NO 139
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 139

Asp Ser Ser Ser Gly Trp Phe Phe Ile Asp Tyr
1 5 10

<210> SEQ ID NO 140
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 140

Asp Ser Ser Ser Gly Trp Phe Phe Ile Asp Tyr
1 5 10

<210> SEQ ID NO 141
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 141

Ser Arg Tyr Ser Ser Ser Pro Phe Arg Gly Gly Leu Asp Val
1 5 10

<210> SEQ ID NO 142
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 142

Asp Ser Ser Ser Gly Trp Phe Phe Ile Asp Tyr
1 5 10

<210> SEQ ID NO 143
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 143

Thr Tyr Pro Tyr Gly Gly Gly Thr Tyr Ala Phe Asp Tyr
1 5 10

<210> SEQ ID NO 144
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 144

Asn Ala Phe Asp Tyr
1 5

<210> SEQ ID NO 145
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 145

Ser Ala Lys Ser Gly Trp Lys Ser Thr Phe Asp Val
1 5 10

<210> SEQ ID NO 146

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<211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 146

Asp Ser Ser Ser Gly Trp Leu Phe Ile Asp Tyr
 1 5 10

<210> SEQ ID NO 147
 <211> LENGTH: 14
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 147

Ser Arg Tyr Ser Ser Ser Pro Phe Arg Gly Gly Leu Asp Val
 1 5 10

<210> SEQ ID NO 148
 <211> LENGTH: 14
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 148

Ser Arg Tyr Ser Ser Ser Pro Phe Arg Gly Gly Leu Asp Val
 1 5 10

<210> SEQ ID NO 149
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 149

Asp Ser Ser Ser Gly Trp Leu Phe Ile Asp Tyr
 1 5 10

<210> SEQ ID NO 150
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 150

Asp Ser Ser Ser Gly Trp Leu Phe Ile Asp Tyr
 1 5 10

<210> SEQ ID NO 151
 <211> LENGTH: 14
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 151

Ser Arg Tyr Ser Ser Ser Pro Phe Arg Gly Gly Leu Asp Val
 1 5 10

<210> SEQ ID NO 152
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 152

Gln Met Ile Met Ala Ala Arg Cys
 1 5

<210> SEQ ID NO 153
 <211> LENGTH: 9
 <212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 153

Asp Ser Ser Ser Gly Trp Phe Phe Ile
1 5

<210> SEQ ID NO 154

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 154

Asp Ser Ser Ser Gly Trp Phe Phe Ile
1 5

<210> SEQ ID NO 155

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 155

Val Asp His Lys Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 156

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 156

Val Asp His Lys Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 157

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 157

Val Asp His Lys Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 158

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 158

Val Asp His Lys Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 159

<211> LENGTH: 14

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 159

Leu Leu Arg Gly Gly Ser Thr Tyr Leu Asp Ala Phe Asp Asn
1 5 10

<210> SEQ ID NO 160

<211> LENGTH: 14

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 160

Leu Leu Arg Gly Gly Ser Thr Tyr Leu Asp Ala Phe Asp Asn
1 5 10

<210> SEQ ID NO 161

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 161

Gly Trp Gly Val Phe Asp Ile
1 5

<210> SEQ ID NO 162

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 162

Val Asp His Asn Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 163

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 163

Val Asp His Asn Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 164

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 164

Val Asp His Asn Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 165

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 165

Val Asp His Asn Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 166

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 166

Val Asp His Asn Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 167

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 167

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Val	Asp	His	Asn	Trp	Asp	Leu	Pro	Phe	Asp	Tyr
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<210> SEQ ID NO 168
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 168

Val	Asp	His	Asn	Trp	Asp	Leu	Pro	Phe	Asp	Tyr
1			5						10	

<210> SEQ ID NO 169
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 169

Val	Asp	His	Asn	Trp	Asp	Leu	Pro	Phe	Asp	Tyr
1			5						10	

<210> SEQ ID NO 170
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 170

Val	Asp	His	Asn	Trp	Asp	Leu	Pro	Phe	Asp	Tyr
1			5						10	

<210> SEQ ID NO 171
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 171

Val	Asp	His	Asn	Trp	Asp	Leu	Pro	Phe	Asp	Tyr
1			5						10	

<210> SEQ ID NO 172
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 172

Val	Asp	His	Asn	Trp	Asp	Leu	Pro	Phe	Asp	Tyr
1			5						10	

<210> SEQ ID NO 173
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 173

Val	Asp	His	Asn	Trp	Asp	Leu	Pro	Phe	Asp	Tyr
1			5						10	

<210> SEQ ID NO 174
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 174

Val	Asp	His	Asn	Trp	Asp	Leu	Pro	Phe	Asp	Tyr
1			5						10	

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<210> SEQ ID NO 175
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 175

Val Asp His Lys Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 176
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 176

Val Asp His Lys Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 177
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 177

Val Asp His Lys Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 178
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 178

Val Asp His Lys Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 179
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 179

Val Asp His Lys Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 180
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 180

Val Asp His Lys Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 181
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 181

Val Asp His Lys Trp Asp Leu Pro Phe Asp Tyr
1 5 10

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<210> SEQ ID NO 182
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 182

Val Asp His Asn Trp Asp Leu Pro Phe Asp Tyr
 1 5 10

<210> SEQ ID NO 183
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 183

Val Asp His Asn Trp Asp Leu Pro Phe Asp Tyr
 1 5 10

<210> SEQ ID NO 184
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 184

Val Asp His Asn Trp Asp Leu Pro Phe Asp Tyr
 1 5 10

<210> SEQ ID NO 185
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 185

Val Asp His Asn Trp Asp Leu Pro Phe Asp Tyr
 1 5 10

<210> SEQ ID NO 186
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 186

Val Asp His Asn Trp Asp Leu Pro Phe Asp Tyr
 1 5 10

<210> SEQ ID NO 187
 <211> LENGTH: 12
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 187

Tyr Val Ala Asp Thr Ser Lys Asp Val Phe Asp Ile
 1 5 10

<210> SEQ ID NO 188
 <211> LENGTH: 10
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 188

Val Ala Ser Thr Ala Leu Tyr Phe Asp Asn
 1 5 10

<210> SEQ ID NO 189
 <211> LENGTH: 13

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 189
Gly Val Tyr Asn Trp Asn Ser Ala Ala Lys Phe Asp Tyr
1 5 10

<210> SEQ ID NO 190
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 190

Thr Tyr Tyr Tyr Val Tyr Tyr Asn Tyr Met Asp Val
1 5 10

<210> SEQ ID NO 191
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 191

Val Ala His Gly Trp His Leu Ser Phe Asp Tyr
1 5 10

<210> SEQ ID NO 192
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 192

Ser Leu Phe Arg Val Arg Gly Val Phe Phe Asp Tyr
1 5 10

<210> SEQ ID NO 193
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 193

Ser Leu Phe Arg Val Arg Gly Val Phe Phe Asp Tyr
1 5 10

<210> SEQ ID NO 194
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 194

Gly Pro Ala Gly Leu Gln Leu Ser Leu Asp Ile
1 5 10

<210> SEQ ID NO 195
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 195

Val Asp His Arg Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 196
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 196

Val	Asp	His	Lys	Trp	Asp	Leu	Pro	Phe	Asp	Tyr
1			5						10	

<210> SEQ ID NO 197

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 197

Val	Asp	His	Lys	Trp	Asp	Leu	Pro	Phe	Asp	Tyr
1			5						10	

<210> SEQ ID NO 198

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 198

Val	Asp	His	Lys	Trp	Asp	Leu	Pro	Phe	Asp	Tyr
1			5						10	

<210> SEQ ID NO 199

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 199

Val	Asp	His	Lys	Trp	Asp	Leu	Pro	Phe	Asp	Tyr
1			5						10	

<210> SEQ ID NO 200

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 200

Ala	Arg	Asp	Tyr	Tyr	Phe	Gly	Met	Asp	Val
1			5						10

<210> SEQ ID NO 201

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 201

Gly	Pro	Ala	Gly	Leu	Gln	Leu	Ser	Leu	Asp	Ile
1			5						10	

<210> SEQ ID NO 202

<211> LENGTH: 12

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 202

Asp	Arg	Ser	Lys	Leu	Asn	Ala	Gly	Tyr	Phe	Asp	Ser
1			5							10	

<210> SEQ ID NO 203

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 203

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Thr Lys Tyr Ser Ser Ile Val Phe Asp Leu
1 5 10

<210> SEQ ID NO 204
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 204

Phe Arg Phe Leu Val Trp Tyr Gly Glu Ala Tyr Phe Asp Tyr
1 5 10

<210> SEQ ID NO 205
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 205

Val Arg Gly Gln Leu Leu Ala Phe Asp Ile
1 5 10

<210> SEQ ID NO 206
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 206

Val Asp His Lys Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 207
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 207

Val Asp His Lys Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 208
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 208

Gly Pro Ala Gly Leu Gln Leu Ser Leu Asp Ile
1 5 10

<210> SEQ ID NO 209
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 209

Thr Lys Tyr Ser Ser Ile Val Phe Asp Leu
1 5 10

<210> SEQ ID NO 210
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 210

Ala Val Trp Asp Asp Ser Leu Asn Gly His

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<210> SEQ ID NO 211
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 211
Thr Lys Tyr Ser Ser Ile Val Phe Asp Leu
1 5 10

<210> SEQ ID NO 212
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 212
Leu Asp His Lys Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 213
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 213
Val Asp His Asn Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 214
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 214
Glu Tyr Tyr Tyr Arg Trp Gly Ser Tyr Ala Asn
1 5 10

<210> SEQ ID NO 215
<211> LENGTH: 11
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 215
Val Asp His Lys Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 216
<211> LENGTH: 11
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 216
Val Asp His Asn Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 217
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 217
Ser Leu Phe Arg Val Arg Gly Val Phe Phe Asp Tyr
1 5 10

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<210> SEQ ID NO 218
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 218

Ser Leu Phe Arg Val Arg Gly Val Phe Phe Asp Tyr
1 5 10

<210> SEQ ID NO 219
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 219

Ser Leu Phe Arg Val Arg Gly Val Phe Phe Asp Tyr
1 5 10

<210> SEQ ID NO 220
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 220

Asp Leu Gly Val Gly Arg Tyr Phe Asp Tyr
1 5 10

<210> SEQ ID NO 221
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 221

Asp Leu Gly Val Gly Arg Tyr Phe Asp Tyr
1 5 10

<210> SEQ ID NO 222
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 222

Ser Leu Phe Arg Val Arg Gly Val Phe Phe Asp Tyr
1 5 10

<210> SEQ ID NO 223
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 223

Asp Arg Ser Lys Leu Asn Ala Gly Tyr Phe Asp Ser
1 5 10

<210> SEQ ID NO 224
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 224

Asp Arg Ser Lys Leu Asn Ala Gly Tyr Phe Asp Ser
1 5 10

<210> SEQ ID NO 225

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<211> LENGTH: 11
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 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 225

Leu Asp His Asn Trp Asp Leu Pro Phe Asp Tyr
 1 5 10

<210> SEQ ID NO 226
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 226

Leu Asp His Asn Trp Asp Leu Pro Phe Asp Tyr
 1 5 10

<210> SEQ ID NO 227
 <211> LENGTH: 11
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<400> SEQUENCE: 227

Leu Asp His Asn Trp Asp Leu Pro Phe Asp Tyr
 1 5 10

<210> SEQ ID NO 228
 <211> LENGTH: 10
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 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 228

Thr Lys Tyr Ser Ser Ile Val Phe Asp Leu
 1 5 10

<210> SEQ ID NO 229
 <211> LENGTH: 10
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 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 229

Thr Lys Tyr Ser Ser Ile Val Phe Asp Leu
 1 5 10

<210> SEQ ID NO 230
 <211> LENGTH: 10
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<400> SEQUENCE: 230

Thr Lys Tyr Ser Ser Ile Val Phe Asp Leu
 1 5 10

<210> SEQ ID NO 231
 <211> LENGTH: 10
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens.

<400> SEQUENCE: 231

Leu Asp His Asn Trp Asn Leu Pro Phe Asp
 1 5 10

<210> SEQ ID NO 232
 <211> LENGTH: 9
 <212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 232

Val Gly Gly Ala Ile Arg Phe Asp Ser
1 5

<210> SEQ ID NO 233

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 233

Ser Val Gly Arg Ser Leu Ala Phe Asp Ile
1 5 10

<210> SEQ ID NO 234

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 234

Arg Thr Gly Asp Cys Ser Tyr Thr Ser Cys Tyr
1 5 10

<210> SEQ ID NO 235

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 235

Gly Pro Ala Gly Leu Gln Leu Ser Leu Asp Ile
1 5 10

<210> SEQ ID NO 236

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 236

Gly Pro Ala Gly Leu Gln Leu Ser Leu Asp Ile
1 5 10

<210> SEQ ID NO 237

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 237

Val Asp His Lys Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 238

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 238

Phe Thr Gly Trp Tyr Gly Ala Phe Asp Ile
1 5 10

<210> SEQ ID NO 239

<211> LENGTH: 13

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 239

Asp Arg Tyr Asn Met Val Gly Val Leu Arg Pro Asp Ser
1 5 10

<210> SEQ ID NO 240

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 240

Gln Ile Trp Gly Arg Phe Glu Tyr
1 5

<210> SEQ ID NO 241

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 241

Gln Ile Trp Gly Arg Phe Glu Tyr
1 5

<210> SEQ ID NO 242

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 242

Gly Tyr Asp Phe Trp Ser Gly Phe Asp Tyr
1 5 10

<210> SEQ ID NO 243

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 243

Gly Trp Gly Val Phe Asp Met
1 5

<210> SEQ ID NO 244

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 244

Val Asp His Lys Trp Asp Leu Pro Phe Asp Phe
1 5 10

<210> SEQ ID NO 245

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 245

Ala Arg Ala Leu Phe Arg Val Ser Gly Pro Tyr
1 5 10

<210> SEQ ID NO 246

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 246

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Asp His Pro Tyr Asn Trp Asn Tyr Phe Asp Tyr
1 5 10

<210> SEQ ID NO 247
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 247

Gly Ala Pro Ala Val Arg His Gly Phe Asp Tyr
1 5 10

<210> SEQ ID NO 248
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 248

Val Asp His Lys Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 249
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 249

Phe Gly Thr Gly Ser Ser Leu Glu Val
1 5

<210> SEQ ID NO 250
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 250

Gln Ala Phe Ala Arg Phe Glu Phe
1 5

<210> SEQ ID NO 251
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 251

Asn Leu Gln Asp Ile Val Ala Thr Ile Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 252
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 252

Val Asp His Asn Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 253
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 253

Gly Asp Pro Glu Glu Leu Arg Ser Asp Ser Tyr Phe Tyr Tyr Gly Met
1 5 10 15

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Asp Val

<210> SEQ ID NO 254
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 254

Leu Asp His Lys Trp Asp Leu Pro Phe Asp His
 1 5 10

<210> SEQ ID NO 255
 <211> LENGTH: 10
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 255

Thr Lys Tyr Ser Ser Val Ala Phe Asp Leu
 1 5 10

<210> SEQ ID NO 256
 <211> LENGTH: 14
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <220> FEATURE:
 <221> NAME/KEY: misc_feature
 <222> LOCATION: (14)..(14)
 <223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
 <400> SEQUENCE: 256

Leu Leu Arg Gly Gly Ser Thr Tyr Leu Asp Ala Phe Asp Xaa
 1 5 10

<210> SEQ ID NO 257
 <211> LENGTH: 14
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 257

Gly Val Tyr Gly Gly Gly Ser Ala Gly Leu Tyr Phe Asp Val
 1 5 10

<210> SEQ ID NO 258
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 258

Gly Glu Met Ala Thr Ile Arg Tyr
 1 5

<210> SEQ ID NO 259
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 259

Val Asp His Lys Trp Asp Leu Pro Phe Asp Tyr
 1 5 10

<210> SEQ ID NO 260
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 260

Val Asp His Asn Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 261

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 261

Ala Ser Ser Trp Tyr Leu Val Phe Asp Ile
1 5 10

<210> SEQ ID NO 262

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 262

Ala Ser Ser Trp Tyr Leu Val Phe Asp Ile
1 5 10

<210> SEQ ID NO 263

<211> LENGTH: 12

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 263

Ser Leu Phe Arg Val Arg Gly Val Phe Phe Asp Tyr
1 5 10

<210> SEQ ID NO 264

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 264

Val Asp His Asn Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 265

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 265

Val Asp His Asn Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 266

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 266

Val Asp Arg Arg Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 267

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 267

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Val Asp His Lys Trp Asp Leu Pro Phe Asp Phe
1 5 10

<210> SEQ ID NO 268
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 268

Gly Gly Pro Pro Phe Gly Ser Ser Tyr Asp Val
1 5 10

<210> SEQ ID NO 269
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 269

Pro Thr Tyr Gly Pro Gly Ser Phe Leu Ile Asp His
1 5 10

<210> SEQ ID NO 270
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 270

Thr Arg Gly Tyr Ser Leu Tyr Phe Asp Ser
1 5 10

<210> SEQ ID NO 271
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 271

Val Asp His Asn Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 272
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 272

Gly Pro Ala Gly Leu Gln Leu Ser Leu Asp Ile
1 5 10

<210> SEQ ID NO 273
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 273

Gly Pro Ala Gly Leu Gln Leu Ser Leu Asp Ile
1 5 10

<210> SEQ ID NO 274
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 274

Val Asp His Lys Trp Asp Leu Pro Phe Asp Tyr
1 5 10

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<210> SEQ ID NO 275
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 275

Ala Gly Gly Ser Ser Leu Val Phe Asp Ser
1 5 10

<210> SEQ ID NO 276
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 276

Asp Gly Pro Ser Asn Tyr Met Asp Val
1 5

<210> SEQ ID NO 277
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 277

Val Asp His Asn Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 278
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 278

Asp Gly Asp Tyr Ser Ser Ser Ser Leu Asp Tyr
1 5 10

<210> SEQ ID NO 279
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 279

Val Arg Val Pro Gly Arg Asp Gly Met Asp Val
1 5 10

<210> SEQ ID NO 280
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 280

Gly Ser Gly Ser Tyr Ile Ala Phe Asp Ile
1 5 10

<210> SEQ ID NO 281
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 281

Thr Thr Val Thr Thr Glu Ser Asp Trp Phe Asp Leu
1 5 10

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<210> SEQ ID NO 282
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 282

Val Asp His Asn Trp Asp Leu Pro Phe Asp Tyr
 1 5 10

<210> SEQ ID NO 283
 <211> LENGTH: 14
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 283

Gly Val Tyr Gly Gly Gly Ser Ala Gly Leu Tyr Phe Asp Val
 1 5 10

<210> SEQ ID NO 284
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 284

Gly Pro Ser Gly Leu Leu Leu Gly Leu Asp Val
 1 5 10

<210> SEQ ID NO 285
 <211> LENGTH: 10
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 285

Val Ala Ser Thr Ala Leu Tyr Phe Asp Asn
 1 5 10

<210> SEQ ID NO 286
 <211> LENGTH: 10
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 286

Leu Ser Gly Val Thr Leu His Met Asp Val
 1 5 10

<210> SEQ ID NO 287
 <211> LENGTH: 10
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 287

Val Arg Gly Gly Asn Leu Ala Phe Asp Phe
 1 5 10

<210> SEQ ID NO 288
 <211> LENGTH: 12
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 288

Ser Leu Phe Arg Val Arg Gly Val Phe Phe Asp Tyr
 1 5 10

<210> SEQ ID NO 289
 <211> LENGTH: 11

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<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 289

Glu Asp His Lys Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 290

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 290

Gly Ala Leu Ser Ser Phe Asp Ser
1 5

<210> SEQ ID NO 291

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 291

Gln Ile Trp Gly Arg Phe Glu Tyr
1 5

<210> SEQ ID NO 292

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 292

Ala Asp His Asn Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 293

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 293

Ala His Trp Gly Ser Arg Val Asp Tyr
1 5

<210> SEQ ID NO 294

<211> LENGTH: 14

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 294

Leu Leu Arg Gly Gly Ser Thr Tyr Leu Asp Ala Phe Asp Asn
1 5 10

<210> SEQ ID NO 295

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 295

Glu Val Gly Ser Tyr Phe Asp Tyr
1 5

<210> SEQ ID NO 296

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 296

Val Asp His Asn Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 297

<211> LENGTH: 12

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 297

Ser Leu Phe Arg Val Arg Gly Val Phe Asp Tyr
1 5 10

<210> SEQ ID NO 298

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 298

Gly Pro Arg Phe Trp Thr Gly Tyr Tyr Asp Tyr
1 5 10

<210> SEQ ID NO 299

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 299

Ala Ser Trp Asp Asp Ser Leu Asn Gly Arg Val
1 5 10

<210> SEQ ID NO 300

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 300

Ala Ser Trp Asp Asp Ser Leu Lys Ser Arg Val
1 5 10

<210> SEQ ID NO 301

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 301

Ala Ser Trp Asp Asp Ser Val Asn Gly Arg Val
1 5 10

<210> SEQ ID NO 302

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 302

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
1 5 10

<210> SEQ ID NO 303

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 303

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Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
1 5 10

<210> SEQ ID NO 304
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 304

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
1 5 10

<210> SEQ ID NO 305
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 305

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
1 5 10

<210> SEQ ID NO 306
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 306

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
1 5 10

<210> SEQ ID NO 307
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 307

Ala Ser Trp Asp Asp Ser Leu Asn Gly Arg Val
1 5 10

<210> SEQ ID NO 308
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 308

Ala Ser Trp Asp Asp Ser Leu Asn Gly Arg Val
1 5 10

<210> SEQ ID NO 309
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 309

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
1 5 10

<210> SEQ ID NO 310
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 310

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val

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1 5 10

<210> SEQ ID NO 311
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 311

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
 1 5 10

<210> SEQ ID NO 312
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 312

His Ser Arg Asp Ser Ser Gly Asn His Val Leu
 1 5 10

<210> SEQ ID NO 313
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 313

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
 1 5 10

<210> SEQ ID NO 314
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 314

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
 1 5 10

<210> SEQ ID NO 315
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 315

Asn. Ser Arg Asp Ser Ser Gly Asn His Val Val
 1 5 10

<210> SEQ ID NO 316
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 316

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
 1 5 10

<210> SEQ ID NO 317
 <211> LENGTH: 10
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 317

Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val
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<210> SEQ ID NO 318
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 318

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
1 5 10

<210> SEQ ID NO 319
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 319

Ala Ser Trp Asp Asp Ser Leu Asn Gly Arg Val
1 5 10

<210> SEQ ID NO 320
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 320

Ala Ser Trp Asp Asp Ser Leu Asn Gly Arg Val
1 5 10

<210> SEQ ID NO 321
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 321

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
1 5 10

<210> SEQ ID NO 322
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 322

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
1 5 10

<210> SEQ ID NO 323
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 323

Ala Ser Trp Asp Asp Ser Leu Asn Gly Arg Val
1 5 10

<210> SEQ ID NO 324
<211> LENGTH: 11
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 324

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
1 5 10

<210> SEQ ID NO 325

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<211> LENGTH: 11
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<400> SEQUENCE: 325

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
1 5 10

<210> SEQ ID NO 326
<211> LENGTH: 11
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<400> SEQUENCE: 326

Ala Ser Trp Asp Asp Ser Leu Asn Gly Arg Val
1 5 10

<210> SEQ ID NO 327
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 327

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
1 5 10

<210> SEQ ID NO 328
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 328

Ser Ser Tyr Thr Thr Arg Ser Thr Arg Val
1 5 10

<210> SEQ ID NO 329
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<400> SEQUENCE: 329

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
1 5 10

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<400> SEQUENCE: 330

Ala Ser Trp Asp Asp Ser Leu Asn Gly Arg Val
1 5 10

<210> SEQ ID NO 331
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<400> SEQUENCE: 331

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
1 5 10

<210> SEQ ID NO 332
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 332

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
1 5 10

<210> SEQ ID NO 333

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 333

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
1 5 10

<210> SEQ ID NO 334

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 334

Ala Ser Trp Asp Asp Ser Leu Asn Gly Arg Val
1 5 10

<210> SEQ ID NO 335

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 335

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
1 5 10

<210> SEQ ID NO 336

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 336

His Ser Arg Asp Ser Ser Gly Asn His Val Leu
1 5 10

<210> SEQ ID NO 337

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 337

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
1 5 10

<210> SEQ ID NO 338

<211> LENGTH: 11

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 338

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
1 5 10

<210> SEQ ID NO 339

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<400> SEQUENCE: 339

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
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<210> SEQ ID NO 340

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<212> TYPE: PRT

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<400> SEQUENCE: 340

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
1 5 10

<210> SEQ ID NO 341

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<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 341

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
1 5 10

<210> SEQ ID NO 342

<211> LENGTH: 12

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 342

Gln Ser Tyr Asp Ser Ser Leu Gly Gly Tyr Val Ile
1 5 10

<210> SEQ ID NO 343

<211> LENGTH: 12

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 343

Gln Ser Tyr Asp Ser Ser Leu Gly Gly Tyr Val Ile
1 5 10

<210> SEQ ID NO 344

<211> LENGTH: 12

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<400> SEQUENCE: 344

Gln Ser Tyr Asp Ser Ser Leu Gly Gly Tyr Val Ile
1 5 10

<210> SEQ ID NO 345

<211> LENGTH: 12

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 345

Gln Ser Tyr Asp Ser Ser Leu Gly Gly Tyr Val Ile
1 5 10

<210> SEQ ID NO 346

<211> LENGTH: 12

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 346

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Gln Ser Tyr Asp Ser Ser Leu Gly Gly Tyr Val Ile
1 5 10

<210> SEQ ID NO 347
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<400> SEQUENCE: 347

Gln Ser Tyr Asp Ser Ser Leu Gly Gly Tyr Val Ile
1 5 10

<210> SEQ ID NO 348
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Gln Ser Tyr Asp Ser Ser Leu Gly Gly Tyr Val Ile
1 5 10

<210> SEQ ID NO 349
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<400> SEQUENCE: 349

Gln Ser Tyr Asp Ser Ser Leu Gly Gly Tyr Val Ile
1 5 10

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<400> SEQUENCE: 350

Gln Ser Tyr Asp Ser Ser Leu Gly Gly Tyr Val Ile
1 5 10

<210> SEQ ID NO 351
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<400> SEQUENCE: 351

Gln Ser Tyr Asp Ser Ser Leu Gly Gly Tyr Gly Ile
1 5 10

<210> SEQ ID NO 352
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 352

His Ser Tyr Asp Ser Ser Ile Ser Gly Gly Ile
1 5 10

<210> SEQ ID NO 353
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 353

His Ser Tyr Asp Ser Ser Ile Ser Gly Trp Ile
1 5 10

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<210> SEQ ID NO 354
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<400> SEQUENCE: 354

His Ser Tyr Asp Ser Ser Ile Ser Gly Trp Ile
1 5 10

<210> SEQ ID NO 355
<211> LENGTH: 11
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 355

His Ser Tyr Asp Ser Ser Ile Arg Gly Trp Ile
1 5 10

<210> SEQ ID NO 356
<211> LENGTH: 11
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 356

His Ser Tyr Asp Ser Ser Ile Arg Gly Gly Ile
1 5 10

<210> SEQ ID NO 357
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 357

His Ser Tyr Asp Ser Ser Ile Ser Gly Gly Ile
1 5 10

<210> SEQ ID NO 358
<211> LENGTH: 11
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 358

His Ser Tyr Asp Ser Ser Ile Ser Ala Trp Ile
1 5 10

<210> SEQ ID NO 359
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 359

His Ser Tyr Asp Ser Ser Ile Ser Gly Trp Ile
1 5 10

<210> SEQ ID NO 360
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<400> SEQUENCE: 360

His Ser Tyr Asp Ser Ser Ile Ser Gly Trp Ile
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<210> SEQ ID NO 361
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<400> SEQUENCE: 361

His Ser Tyr Asp Ser Ser Ile Ser Gly Trp Ile
1 5 10

<210> SEQ ID NO 362
<211> LENGTH: 12
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 362

Gln Ser Tyr Asp Ser Ser Leu Gly Gly Tyr Val Ile
1 5 10

<210> SEQ ID NO 363
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 363

His Ser Tyr Asp Ser Ser Ile Ser Gly Trp Ile
1 5 10

<210> SEQ ID NO 364
<211> LENGTH: 11
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 364

His Ser Tyr Asp Ser Ser Ile Ser Gly Trp Ile
1 5 10

<210> SEQ ID NO 365
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<400> SEQUENCE: 365

Gln Ser Tyr Asp Ser Ser Leu Gly Gly Tyr Val Ile
1 5 10

<210> SEQ ID NO 366
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 366

His Ser Tyr Asp Ser Ser Ile Ser Gly Trp Ile
1 5 10

<210> SEQ ID NO 367
<211> LENGTH: 11
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 367

His Ser Tyr Asp Ser Ser Ile Ser Gly Trp Ile
1 5 10

<210> SEQ ID NO 368
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<212> TYPE: PRT
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<400> SEQUENCE: 368
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1 5 10

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<400> SEQUENCE: 369
Gln Ser Tyr Asp Ser Ser Leu Gly Gly Tyr Val Ile
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<400> SEQUENCE: 370
Gln Ser Tyr Asp Ser Ser Leu Gly Gly Tyr Val Ile
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His Ser Tyr Asp Ser Ser Ile Ser Gly Trp Ile
1 5 10

<210> SEQ ID NO 372
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<400> SEQUENCE: 372
His Ser Tyr Asp Ser Ser Ile Ser Gly Trp Ile
1 5 10

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<400> SEQUENCE: 373
Gln Ser Tyr Asp Ser Ser Leu Gly Gly Tyr Val Ile
1 5 10

<210> SEQ ID NO 374
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<400> SEQUENCE: 374
Gln Ser Tyr Asp Ser Ser Leu Gly Gly Tyr Val Ile
1 5 10

<210> SEQ ID NO 375
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<400> SEQUENCE: 375

His Ser Tyr Asp Ser Ser Ile Ser Gly Trp Ile
1 5 10

<210> SEQ ID NO 376

<211> LENGTH: 12

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 376

Gln Ser Tyr Asp Ser Ser Leu Gly Gly Tyr Val Ile
1 5 10

<210> SEQ ID NO 377

<211> LENGTH: 12

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 377

Gln Ser Tyr Asp Ser Glu Leu Ser Gly Ser Glu Leu
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<210> SEQ ID NO 378

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 378

Asn Ser Leu Asp Ser Arg Gly Gln Arg Val Ile
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<210> SEQ ID NO 379

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 379

Ala Leu Tyr Leu Gly Gly Gly Leu Ser Trp Val
1 5 10

<210> SEQ ID NO 380

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 380

Ala Ala Trp Asp Asp Ser Leu Ser Ala Tyr Val
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<210> SEQ ID NO 381

<211> LENGTH: 12

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 381

Gln Ser Tyr Asp Ser Ser Leu Gly Gly Tyr Val Ile
1 5 10

<210> SEQ ID NO 382

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 382

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His Ser Tyr Asp Ser Ser Ile Ser Gly Trp Ile
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<210> SEQ ID NO 383
<211> LENGTH: 11
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<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 383

His Ser Tyr Asp Ser Ser Ile Ser Gly Trp Ile
1 5 10

<210> SEQ ID NO 384
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Gln Ser Tyr Asp Ser Ser Leu Gly Gly Tyr Val Ile
1 5 10

<210> SEQ ID NO 385
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Gln Ser Tyr Asp Ser Ser Leu Gly Gly Tyr Val Ile .
1 5 10

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
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His Ser Tyr Asp Ser Ser Ile Ser Gly Trp Ile
1 5 10

<210> SEQ ID NO 387
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
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Gln Ser Phe Asp Asn Arg Leu Arg Gly Phe Val Val
1 5 10

<210> SEQ ID NO 388
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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 388

Gln Ser Tyr Asp Ser Ser Leu Gly Gly Tyr Val Ile
1 5 10

<210> SEQ ID NO 389
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
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Gln Ser Tyr Asp Ser Ser Leu Gly Gly Tyr Val Ile

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<210> SEQ ID NO 390
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 390
Ala Thr Trp Asp Asp Asn Leu Asn Gly Trp Val
1 5 10

<210> SEQ ID NO 391
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<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 391
Ala Thr Trp Asp Asp Ser Leu Asn Gly Trp Val
1 5 10

<210> SEQ ID NO 392
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<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 392
Ala Thr Trp Asp Asp Ser Leu Asn Gly Trp Val
1 5 10

<210> SEQ ID NO 393
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 393
Ala Ala Trp Asp Asp Ser Leu Asn Gly Trp Val
1 5 10

<210> SEQ ID NO 394
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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 394
Gln Val Trp Asp Arg Ser Asn Gly His Val Val
1 5 10

<210> SEQ ID NO 395
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 395
Gln Val Trp Asp Arg Ser Asn Gly His Val Val
1 5 10

<210> SEQ ID NO 396
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 396
Ala Ala Trp Asp Asp Ser Leu Asp Gly Val Val
1 5 10

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<210> SEQ ID NO 397
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 397

Ser Ala Trp Asp Asp Ser Leu Asn Gly Trp Val
1 5 10

<210> SEQ ID NO 398
<211> LENGTH: 11
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 398

Ala Ser Trp Asp Asp Asp Leu Asn Gly Trp Val
1 5 10

<210> SEQ ID NO 399
<211> LENGTH: 11
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 399

Ala Val Trp Asp Asp Arg Met Asn Gly Trp Glu
1 5 10

<210> SEQ ID NO 400
<211> LENGTH: 11
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 400

Ala Ala Trp Asp Asp Ser Leu Asn Gly Trp Val
1 5 10

<210> SEQ ID NO 401
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 401

Ala Val Trp Asp Asp Arg Leu Asn Gly Trp Glu
1 5 10

<210> SEQ ID NO 402
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 402

Val Asp His Asn Trp Asp Leu Pro Phe Asp
1 5 10

<210> SEQ ID NO 403
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 403

Ala Ala Trp Asp Asp Ser Leu Ser Gly Trp Met
1 5 10

<210> SEQ ID NO 404

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<211> LENGTH: 11
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 404
Ala Ser Trp Asp Asp Asp Leu Lys Ser Trp Val
1 5 10

<210> SEQ ID NO 405
<211> LENGTH: 11
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 405

Ala Ala Trp Asp Asp Ser Leu Ser Gly Trp Val
1 5 10

<210> SEQ ID NO 406
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 406

Ala Thr Trp Asp Asp Ser Leu Lys Gly Trp Val
1 5 10

<210> SEQ ID NO 407
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 407

Gln Gln Ser Lys Ser Ile Pro Ile Thr
1 5

<210> SEQ ID NO 408
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 408

Val Ala Trp Asp Asp Ser Leu Asn Gly Trp Met
1 5 10

<210> SEQ ID NO 409
<211> LENGTH: 11
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 409

Ala Ala Trp Asp Asp Ser Leu Ser Gly Trp Val
1 5 10

<210> SEQ ID NO 410
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 410

Ala Ala Trp Asp Asp Ser Leu Lys Gly Trp Val
1 5 10

<210> SEQ ID NO 411
<211> LENGTH: 11
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 411

Ser Ala Trp Asp Asp Gly Leu Ser Gly Trp Val
1 5 10

<210> SEQ ID NO 412

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 412

Ala Thr Trp Asp Asp Ser Leu Pro Gly Leu Val
1 5 10

<210> SEQ ID NO 413

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 413

Glu Ala Trp Asp Asp Ser Leu Ser Gly Pro Ala
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<210> SEQ ID NO 414

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 414

Ala Ala Trp Asp Asp Asn Leu Ser Gly Pro
1 5 10

<210> SEQ ID NO 415

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 415

Gln Gln Thr Tyr Arg Thr Pro Ile Thr
1 5

<210> SEQ ID NO 416

<211> LENGTH: 12

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 416

Gly Thr Trp Asp Ser Arg Leu Tyr Val Gly Gln Val
1 5 10

<210> SEQ ID NO 417

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 417

Ala Ala Trp Asp Asp Ser Leu Asn Gly Trp Val
1 5 10

<210> SEQ ID NO 418

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 418

Ala Ala Trp Asp Asp Ser Leu Asn Gly Trp Val
1 5 10

<210> SEQ ID NO 419

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 419

Ala Thr Trp Asp Asp Ser Leu Asn His Trp Val
1 5 10

<210> SEQ ID NO 420

<211> LENGTH: 12

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 420

Ala Ala Trp Asp Asp Ser Leu Asn Gly His Trp Val
1 5 10

<210> SEQ ID NO 421

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 421

Ala Ala Trp Asp Asp Ser Leu Ser Gly Val Leu
1 5 10

<210> SEQ ID NO 422

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 422

Asn Ser Arg Asp Ser Ser Gly Asn Val Val
1 5 10

<210> SEQ ID NO 423

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 423

Ala Ser Trp Asp Asp Thr Leu Lys Gly Gly Val
1 5 10

<210> SEQ ID NO 424

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 424

Gln Ser Tyr Asp Asn Ser Leu Ser Gly Ser Glu
1 5 10

<210> SEQ ID NO 425

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 425

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Asn	Ser	Arg	Asp	Ser	Ser	Gly	Asp	Pro	Val	Thr
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<210> SEQ ID NO 426
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 426

Ser	Ala	Trp	Asp	Asp	Ser	Leu	Lys	Gly	Trp	Val
1			5						10	

<210> SEQ ID NO 427
 <211> LENGTH: 12
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 427

Ala	Ser	Arg	Asp	Ser	Ser	Ala	Asn	Gln	His	Trp	Val
1			5						10		

<210> SEQ ID NO 428
 <211> LENGTH: 9
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 428

Gln	Ser	Tyr	Asp	Ser	Ser	Thr	Gly	Ile
1			5					

<210> SEQ ID NO 429
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 429

Ala	Ala	Trp	Asp	Asp	Ser	Leu	Asn	Gly	Leu	Val
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<210> SEQ ID NO 430
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 430

Ser	Thr	Trp	Asp	Gly	Ser	Leu	Asn	Gly	Trp	Val
1			5						10	

<210> SEQ ID NO 431
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 431

Ala	Ala	Trp	Asp	Asp	Ser	Leu	Asn	Gly	Trp	Val
1			5						10	

<210> SEQ ID NO 432
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 432

Ser	Thr	Trp	Asp	Asp	Ser	Leu	Arg	Gly	Val	Val
1			5						10	

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<210> SEQ ID NO 433
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 433

Ala Val Trp Asp Asp Ser Leu Asn Gly Trp Val
1 5 10

<210> SEQ ID NO 434
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 434

Ala Pro Trp Asp Asp Ser Leu Asn Gly Trp Val
1 5 10

<210> SEQ ID NO 435
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 435

Ser Ala Trp Asp Asp Ser Leu His Gly Pro Val
1 5 10

<210> SEQ ID NO 436
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 436

Ala Ala Trp Asp Asp Ser Leu Asn Gly Val Val
1 5 10

<210> SEQ ID NO 437
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 437

Gln Ser Tyr Asp Asn Ser Leu Ser Ala Trp
1 5 10

<210> SEQ ID NO 438
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 438

Ala Ala Trp Asp Asp Ser Leu Asn Val Val Val
1 5 10

<210> SEQ ID NO 439
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 439

Ser Ser Arg Asp Asn Ser Gly Asp Arg Leu Val Leu
1 5 10

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<210> SEQ ID NO 440
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 440

Ala Ala Trp Asp Asp Ser Leu Asn Gly Trp Val
1 5 10

<210> SEQ ID NO 441
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 441

Ala Thr Trp Asp Asp Ser Leu Arg Gly Trp Val
1 5 10

<210> SEQ ID NO 442
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 442

Ala Thr Trp Asp Asp Ser Val Arg Gly Trp Val
1 5 10

<210> SEQ ID NO 443
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 443

Ala Thr Trp Asp Asp Ser Leu Ser Gly Trp Val
1 5 10

<210> SEQ ID NO 444
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 444

Ala Ala Trp Asp Asp Ser Leu Asn Ala Val Leu
1 5 10

<210> SEQ ID NO 445
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 445

Val Asp Arg Arg Trp Asp Leu Pro Phe Asp Tyr
1 5 10

<210> SEQ ID NO 446
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 446

Ala Ser Trp Asp Asp Ser Leu Asn Gly Val
1 5 10

<210> SEQ ID NO 447
<211> LENGTH: 11

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 447
Glu Ala Trp Asp Asp Ser Leu Ser Gly Pro Ala
1 5 10

<210> SEQ ID NO 448
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 448

Gly Thr Trp Asp Ser Arg Leu Ser Ala Val Val
1 5 10

<210> SEQ ID NO 449
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 449

Asn Ser Arg Asp Ser Ser Gly Asn Pro Val Val
1 5 10

<210> SEQ ID NO 450
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 450

Thr Ala Trp Asp Asp Ser Leu Asn Gly Trp Val
1 5 10

<210> SEQ ID NO 451
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 451

Ala Ala Trp Asp Asp Ile Leu Asn Gly Trp Val
1 5 10

<210> SEQ ID NO 452
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 452

Asn Ser Arg Asp Ser Ser Gly Asn His Val Val
1 5 10

<210> SEQ ID NO 453
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<400> SEQUENCE: 453

Gln Ala Trp Asp Ser Ser Thr Thr Trp Glu
1 5 10

<210> SEQ ID NO 454
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 454

Glu	Thr	Trp	Asp	Thr	Ser	Leu	Ser	Val	Leu	Val
1				5					10	

<210> SEQ ID NO 455

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 455

Ser	Ser	Arg	Asp	Asn	Ser	Gly	Asp	Pro	Leu
1				5					10

<210> SEQ ID NO 456

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 456

Ser	Ser	Arg	Asp	Asn	Ser	Gly	Asp	Pro	Leu
1				5					10

<210> SEQ ID NO 457

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 457

Asn	Ser	Arg	Asp	Ser	Ser	Gly	Asn	His	Trp	Val
1				5					10	

<210> SEQ ID NO 458

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 458

Gln	Ser	Tyr	Asp	Ser	Ser	Leu	Ser	Ala	Tyr	Val
1				5					10	

<210> SEQ ID NO 459

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 459

Gln	Ser	Tyr	Asp	Ser	Gly	Leu	Ser	Ala	Val	Val
1				5					10	

<210> SEQ ID NO 460

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 460

Ala	Ser	Trp	Asp	Asp	Ser	Leu	Ser	Gly	Trp	Val
1				5					10	

<210> SEQ ID NO 461

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 461

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Ala Thr Trp Asp Asp Ser Leu Ser Gly Leu Leu
1 5 10

<210> SEQ ID NO 462
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 462

Ala Ser Trp Asp Asp Ser Leu Lys Gly Val Val
1 5 10

<210> SEQ ID NO 463
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 463

Ala Ala Trp Asp Asp Arg Leu Ser Gly Pro Val
1 5 10

<210> SEQ ID NO 464
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 464

Ala Ala Trp Asp Asp Ser Leu Asn Gly Met Leu
1 5 10

<210> SEQ ID NO 465
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 465

Ala Ala Trp Asp Asp Ser Leu Asn Gly Pro
1 5 10

<210> SEQ ID NO 466
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 466

Ala Thr Trp Asp Asp Arg Leu Lys Gly Phe Val
1 5 10

<210> SEQ ID NO 467
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 467

Ser Ala Trp Asp Asp Ser Leu Ser Gly Val Val
1 5 10

<210> SEQ ID NO 468
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 468

Ala Ala Trp Asp Asp Ser Leu Asn Gly His Val Val

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1 5 10

<210> SEQ ID NO 469
 <211> LENGTH: 9
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 469

Gln Thr Trp Asp Ser Thr Thr Ala Ser
 1 5

<210> SEQ ID NO 470
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 470

Ser Ala Trp Asp Asp Ser Leu Asn Gly Pro Ala
 1 5 10

<210> SEQ ID NO 471
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 471

Ser Ala Trp Asp Asp Ser Leu Asn Gly Pro Ala
 1 5 10

<210> SEQ ID NO 472
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 472

Ala Thr Trp Asp Asp Thr Leu Ser Gly Leu Val
 1 5 10

<210> SEQ ID NO 473
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 473

Ala Thr Trp Asp Asp Ser Val Asn Gly Pro Ala
 1 5 10

<210> SEQ ID NO 474
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 474

Ser Ser Tyr Ala Arg Ser Asn Asn Phe Gly Val
 1 5 10

<210> SEQ ID NO 475
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 475

Ala Ala Trp Asp Asp Arg Leu Asn Gly Tyr Val
 1 5 10

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<210> SEQ ID NO 476
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 476

Ala Ala Trp Asp Asp Ser Leu Asn Gly Val Val
1 5 10

<210> SEQ ID NO 477
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 477

Gln Val Trp Asp Ser Thr Ser Asp His Arg Ile
1 5 10

<210> SEQ ID NO 478
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 478

Ala Ala Trp Asp Asp Ser Leu Asp Gly Val Val
1 5 10

<210> SEQ ID NO 479
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 479

Ala Ser Trp Asp Asp Ser Leu Asp Gly Trp Val
1 5 10

<210> SEQ ID NO 480
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 480

Ser Ser Tyr Ser Gly Asp Val Asn Phe Ile Val
1 5 10

<210> SEQ ID NO 481
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 481

Gln Gln Leu Asn Arg Tyr Pro Ser Leu
1 5

<210> SEQ ID NO 482
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 482

Gln Gln Tyr Tyr Ser Thr Pro Pro Thr
1 5

<210> SEQ ID NO 483

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<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 483
Ala Thr Trp Asp Asp Ser Leu Lys Gly Phe Val
1 5 10

<210> SEQ ID NO 484
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 484
Ala Ala Trp Asp Asp Ser Leu Asn Gly Val Val
1 5 10

<210> SEQ ID NO 485
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 485
Ser Ser Trp Asp Asp Ser Leu Asn Gly Val Val
1 5 10

<210> SEQ ID NO 486
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 486
Gly Thr Trp Asp Ser Ser Leu Asn Thr Tyr Val
1 5 10

<210> SEQ ID NO 487
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 487
Ser Ala Trp Asp Asp Ser Leu Asn Gly Trp Val
1 5 10

<210> SEQ ID NO 488
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 488
Gln Ser Tyr Asp Ser Ser Leu Ser Gly Ser Trp Val
1 5 10

<210> SEQ ID NO 489
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 489
Glu Ala Trp Asp Asp Ser Leu Ser Gly Pro Ala
1 5 10

<210> SEQ ID NO 490
<211> LENGTH: 11
<212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 490

Ala Thr Trp Asp Asp Ser Leu Asn Gly Val Val
1 5 10

<210> SEQ ID NO 491

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 491

Gln Val Trp Asp Arg Ser Asn Gly His Val Val
1 5 10

<210> SEQ ID NO 492

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 492

Gln Gln Phe Lys Ser Tyr Pro Leu Thr
1 5

<210> SEQ ID NO 493

<211> LENGTH: 10

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 493

Gln Val Trp Asp Asn Ser Ser Gly Trp Val
1 5 10

<210> SEQ ID NO 494

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 494

Ala Thr Trp Asp Asp Ser Leu Asn Gly Trp Val
1 5 10

<210> SEQ ID NO 495

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 495

Ala Ala Trp Asp Ala Ser Leu Thr Ser Trp Val
1 5 10

<210> SEQ ID NO 496

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 496

Ala Ala Trp Asp Asp Ser Leu Asn Gly Val Val
1 5 10

<210> SEQ ID NO 497

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 497

Ala Ala Trp Asp Asp Ser Leu Asn Gly Trp Val
1 5 10

<210> SEQ ID NO 498

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 498

Ala Ala Trp Asp Asp Ser Leu Asn Gly Trp Val
1 5 10

<210> SEQ ID NO 499

<211> LENGTH: 13

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 499

Gly Thr Trp Asp Ser Ser Leu Ser Asp Gly Lys Val Val
1 5 10

<210> SEQ ID NO 500

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 500

Ala Ala Trp Asp Asp Ser Leu Asn Gly Trp Val
1 5 10

<210> SEQ ID NO 501

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 501

Ala Thr Trp Asp Asp Ser Arg Gly Gly Trp Val
1 5 10

<210> SEQ ID NO 502

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 502

Ala Ser Trp Asp Asp Ser Val Gly Ser Trp Val
1 5 10

<210> SEQ ID NO 503

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 503

Ala Ala Trp Asp Asp Ser Leu Asn Gly Trp Val
1 5 10

<210> SEQ ID NO 504

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 504

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Ala Ser Trp Asp Asp Asp Leu Ser Gly Leu Val
1 5 10

<210> SEQ ID NO 505
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 505

Ala Thr Trp Asp Asp Ser Leu Asn Gly Pro Val
1 5 10

<210> SEQ ID NO 506
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 506

Ala Thr Trp Asp Asp Ser Leu Met Val Gly Val
1 5 10

<210> SEQ ID NO 507
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 507

Ala Thr Trp Asp Asp Ser Leu Asn Gly Trp Val
1 5 10

<210> SEQ ID NO 508
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 508

Ala Val Trp Asp Asp Ser Leu Asn Gly Val Ile
1 5 10

<210> SEQ ID NO 509
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 509

Ala Ala Trp Asp Asp Asn Leu Asn Gly Val Val
1 5 10

<210> SEQ ID NO 510
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 510

Ala Ala Trp Asp Asp Ser Leu Lys Gly Trp Val
1 5 10

<210> SEQ ID NO 511
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 511

Ala Val Trp Asp Asp Gly Leu Ser Gly Trp Val
1 5 10

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<210> SEQ ID NO 512
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 512

Gln Gln Tyr Tyr Ser Thr Pro Ile Thr
1 5

<210> SEQ ID NO 513
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 513

Val Ala Trp Asp Asp Ser Leu Asn Gly Trp Val
1 5 10

<210> SEQ ID NO 514
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 514

Gln Ser His Asp Asn Thr Leu Gly Glu Val
1 5 10

<210> SEQ ID NO 515
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 515

Ala Ser Trp Asp Asp Ser Leu Thr Trp Val
1 5 10

<210> SEQ ID NO 516
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 516

Ala Ala Trp Asp Asp Ser Leu Ser Gly Pro Val Val
1 5 10

<210> SEQ ID NO 517
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 517

Asn Ser Arg Asp Ser Ser Gly Asn His Phe Asp Val Val
1 5 10

<210> SEQ ID NO 518
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 518

Ala Thr Trp Asp Asp Ser Leu Asn Gly Phe Val
1 5 10

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<210> SEQ ID NO 519
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 519

Gln Val Trp Asp Asn Ser Ser Gly Trp Val
1 5 10

<210> SEQ ID NO 520
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 520

Ala Val Trp Asp Asp Ser Leu Asn Gly Val Leu
1 5 10

<210> SEQ ID NO 521
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 521

Ala Ala Trp Asp Asp Ser Leu Thr Gly Trp Val
1 5 10

<210> SEQ ID NO 522
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 522

Ala Ala Trp Asp Asp Ser Leu Lys Gly Pro Val
1 5 10

<210> SEQ ID NO 523
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 523

Ala Ala Trp Asp Asp Ser Leu Ser Gly Trp Val
1 5 10

<210> SEQ ID NO 524
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 524

Val Thr Trp Asp Gly Ser Leu Gly Val Val Met
1 5 10

<210> SEQ ID NO 525
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 525

Ala Ala Trp Asp Asp Ser Leu Lys Gly Trp Val
1 5 10

<210> SEQ ID NO 526
<211> LENGTH: 11

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 526

Ala Ala Trp Asp Asp Ser Leu Asn Gly Trp Val
1 5 10

<210> SEQ ID NO 527
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 527

Ala Ala Trp Asp Asp Ser Leu Asn Gly Val Val
1 5 10

<210> SEQ ID NO 528
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 528

Ala Ala Trp Asp Asp Ser Leu Asn Gly Trp Val
1 5 10

<210> SEQ ID NO 529
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 529

Ala Ala Trp Asp Asp Ser Leu Asn Gly Val Val
1 5 10

<210> SEQ ID NO 530
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 530

Gln Val Trp Asp Arg Ser Asn Gly His Val Val
1 5 10

<210> SEQ ID NO 531
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 531

Asn Ser Arg Asp Ser Ser Gly Asn Leu Trp Val
1 5 10

<210> SEQ ID NO 532
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 532

Ala Ala Trp Asp Asp Ser Leu Asn Gly Val Val
1 5 10

<210> SEQ ID NO 533
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 533

Ala Ala Trp Asp Asp Ser Leu Asn Gly Trp Val
 1 5 10

<210> SEQ ID NO 534

<211> LENGTH: 11

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 534

Asn Ser Arg Asp Asn Ser Gly Asn Leu Trp Val
 1 5 10

<210> SEQ ID NO 535

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 535

Gln Gln Ser Leu Thr Ala Trp Thr
 1 5

What is claimed is:

1. An isolated antibody or fragment thereof comprising the amino acid sequences of the VHCDR1 domain (residues 26-35 of SEQ ID NO:53), the VHCDR2 domain (residues 50-66 of SEQ ID NO:53), the VHCDR3 domain (residues 99-106 of SEQ ID NO:53), the VLCDR1 domain (residues 156-168 of SEQ ID NO:53), the VLCDR2 domain (residues 184-190 of SEQ ID NO:53), and the VLCDR3 domain (residues 223-233 of SEQ ID NO:53), of the scFv of SEQ ID NO:53, wherein said antibody or fragment thereof specifically binds protective antigen (PA).

2. The antibody or fragment thereof of claim 1, wherein said antibody or fragment thereof inhibits binding of PA83 to anthrax receptor (ATR).

3. The antibody or fragment thereof of claim 1, wherein said antibody or fragment thereof inhibits an activity selected from the group consisting of:

- (a) binding of PA83 to capillary morphogenesis protein 2 (CMG2);
- (b) protease cleavage of PA83 into PA20 and PA63;
- (c) heptamerization of PA63;
- (d) PA63 binding to edema factor (EF);
- (e) PA63 binding to lethal factor (LF);
- (f) PA-mediated translocation of EF across a cell membrane; and
- (g) PA-mediated translocation of LF across a cell membrane.

4. The antibody or fragment thereof of claim 1 wherein said PA is purified from a bacterial cell culture, and wherein said PA is encoded by a polynucleotide encoding amino acids 1 to 764 of SEQ ID NO:2 operably associated with a regulatory sequence that controls expression of said polynucleotide.

5. The antibody or fragment thereof of claim 1 wherein the antibody or fragment thereof is a monoclonal antibody.

6. The antibody or fragment thereof of claim 1 wherein the antibody or fragment thereof is a human antibody.

7. The antibody or fragment thereof of claim 1 wherein the antibody or fragment thereof is selected from the group consisting of:

- (a) a whole immunoglobulin molecule;
- (b) an scFv;
- (c) a chimeric antibody;
- (d) a Fab fragment;
- (e) an F(ab')₂; and
- (f) a disulfide linked Fv.

8. The antibody or fragment thereof of claim 1 which comprises a heavy chain immunoglobulin constant domain selected from the group consisting of:

- (a) a human IgM constant domain;
- (b) a human IgG1 constant domain;
- (c) a human IgG2 constant domain;
- (d) a human IgG3 constant domain;
- (e) a human IgG4 constant domain; and
- (f) a human IgA constant domain.

9. The antibody or fragment thereof of claim 1 which comprises a light chain immunoglobulin constant domain selected from the group consisting of:

- (a) a human Ig kappa constant domain; and
- (b) a human Ig lambda constant domain.

10. The antibody or fragment thereof of claim 1 wherein the antibody or fragment thereof has a dissociation constant (K_D) of less than or equal to 10^{-9} M.

11. The antibody or fragment thereof of claim 1 wherein the antibody or fragment thereof has a K_D less than or equal to 10^{-10} M.

12. The antibody or fragment thereof of claim 1 wherein the antibody or fragment thereof is conjugated to a detectable label.

13. The antibody or fragment thereof of any one of claim 1 wherein the antibody or fragment thereof is attached to a solid support.

14. The antibody or fragment thereof of claim 1 wherein the antibody or fragment thereof specifically binds PA in a Western blot.

15. The antibody or fragment thereof of claim 1 wherein the antibody or fragment thereof specifically binds PA in an ELISA.

16. An isolated cell that produces the antibody or fragment thereof of claim 1.

17. A method of treatment of anthrax infection or anthrax toxin poisoning comprising administering to an animal the antibody or fragment thereof of claim 1.

18. The method of claim 17 wherein the animal is a human.

19. A method of passive immunization comprising administering to an animal the antibody or fragment thereof of claim 1.

20. The method of claim 17 wherein the antibody or fragment thereof is administered in combination with a second antibody or fragment thereof that specifically binds PA.

21. The method of claim 17 wherein the antibody or fragment thereof is administered in combination with an anti-anthrax agent selected from the group consisting of:

- (a) a soluble form of the anthrax toxin receptor;
- (b) a soluble form of the capillary morphogenesis protein 2 receptor;
- (c) an anti-anthrax toxin receptor antibody;
- (d) an anti-edema factor antibody; and
- (e) an anti-lethal factor antibody.

22. The method of claim 17 wherein the antibody or fragment thereof is administered in combination with an antibiotic.

23. The method of claim 22 wherein the antibiotic is ciprofloxacin hydrochloride.

24. The method of claim 22 wherein the antibiotic is doxycycline.

25. The method of claim 22 wherein the antibiotic is selected from the group consisting of:

- (a) penicillin G procaine;
- (b) amoxicillin;
- (c) ofloxacin; and
- (d) levofloxacin.

26. The method of claim 17 wherein the antibody or fragment thereof is administered in combination with a member selected from the group consisting of:

- (a) an anti-TNF-alpha antibody; and
- (b) an anti-IL-1 beta antibody.

27. A kit comprising the antibody or fragment thereof of claim 1 and a means for administering said antibody to an animal.

28. The kit of claim 27 wherein the animal is a human.

29. An isolated antibody or fragment thereof comprising the amino acid sequence of amino acid residues 1-117 of SEQ ID NO:53 and the amino acid sequence of amino acid residues 134-244 of SEQ ID NO:53 wherein said antibody or fragment thereof specifically binds PA.

30. The antibody or fragment thereof of claim 29 that comprises amino acid residues 1-244 of SEQ ID NO:53.

31. The antibody or fragment thereof of claim 29 that consists of amino acid residues 1-244 of SEQ ID NO:53.

32. The antibody or fragment thereof of claim 29 wherein said PA is purified from a bacterial cell culture, and wherein said PA is encoded by a polynucleotide encoding amino acids 1 to 764 of SEQ ID NO:2 operably associated with a regulatory sequence that controls expression of said polynucleotide.

33. The antibody or fragment thereof of claim 29 wherein the antibody or fragment thereof is a monoclonal antibody.

34. The antibody or fragment thereof of claim 29 wherein the antibody or fragment thereof is a human antibody.

35. The antibody or fragment thereof of claim 29 wherein the antibody or fragment thereof is selected from the group consisting of:

- (a) a whole immunoglobulin molecule;
- (b) an scFv;
- (c) a chimeric antibody;

(d) a Fab fragment;

(e) an F(ab')₂; and

(f) a disulfide linked Fv.

36. The antibody or fragment thereof of claim 29 which comprises a heavy chain immunoglobulin constant domain selected from the group consisting of:

- (a) a human IgM constant domain;
- (b) a human IgG1 constant domain;
- (c) a human IgG2 constant domain;
- (d) a human IgG3 constant domain;
- (e) a human IgG4 constant domain; and
- (f) a human IgA constant domain.

37. The antibody or fragment thereof of claim 29 which comprises a light chain immunoglobulin constant domain selected from the group consisting of:

- (a) a human Ig kappa constant domain; and
- (b) a human Ig lambda constant domain.

38. The antibody or fragment thereof of claim 29 wherein the antibody or fragment thereof is conjugated to a detectable label.

39. The antibody or fragment thereof of any one of claim 29 wherein the antibody or fragment thereof is attached to a solid support.

40. An isolated cell that produces the antibody or fragment thereof of claim 29.

41. A method of treatment of anthrax infection or anthrax toxin poisoning comprising administering to an animal the antibody or fragment thereof of claim 29.

42. The method of claim 41 wherein the animal is a human.

43. A method of passive immunization comprising administering to an animal the antibody or fragment thereof of claim 29.

44. The method of claim 41 wherein the antibody or fragment thereof is administered in combination with a second antibody or fragment thereof that specifically binds PA.

45. The method of claim 41 wherein the antibody or fragment thereof is administered in combination with an anti-anthrax agent selected from the group consisting of:

- (a) a soluble form of the anthrax toxin receptor;
- (b) a soluble form of the capillary morphogenesis protein 2 receptor;
- (c) an anti-anthrax toxin receptor antibody;
- (d) an anti-edema factor antibody; and
- (e) an anti-lethal factor antibody.

46. The method of claim 41 wherein the antibody or fragment thereof is administered in combination with an antibiotic.

47. The method of claim 46 wherein the antibiotic is ciprofloxacin hydrochloride.

48. The method of claim 46 wherein the antibiotic is doxycycline.

49. The method of claim 46 wherein the antibiotic is selected from the group consisting of:

- (a) penicillin G procaine;
- (b) amoxicillin;
- (c) ofloxacin; and
- (d) levofloxacin.

50. The method of claim 41 wherein the antibody or fragment thereof is administered in combination with a member selected from the group consisting of:

- (a) an anti-TNF-alpha antibody; and
- (b) an anti-IL-1 beta antibody.

51. A kit comprising the antibody or fragment thereof of claim 29.

52. The cell line contained in ATCC Deposit Number PTA-4796.

53. The antibody produced by the cell line of claim 52.

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54. The method of claim 41 wherein the antibody or fragment thereof is administered intravenously (IV).

55. The method of claim 41 wherein the antibody or fragment thereof is administered sub-cutaneously (SC).

56. The method of claim 41 wherein the antibody or fragment thereof is administered intramuscularly (IM).

57. The method of claim 41 for treating anthrax infection or anthrax toxin poisoning wherein the antibody or fragment thereof is administered in a quantity in the range of 1 to 100 milligrams per kilogram of the animal's body weight.

58. The method of claim 57 wherein the antibody or fragment thereof is administered in a quantity in the range of 1 to 10 milligrams per kilogram of the animal's body weight.

59. The method of claim 41 for treating anthrax infection or anthrax toxin poisoning wherein the antibody or fragment thereof is administered in a quantity in the range of 0.1 to 20 milligrams per kilogram of the animal's body weight.

60. The method of claim 59 wherein the antibody or fragment thereof is administered in a quantity in the range of 1 to 10 milligrams per kilogram of the animal's body weight.

61. The method of claim 41 that prevents or reduces bacteremia associated with anthrax infection.

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62. The method of claim 17 wherein the antibody or fragment thereof is administered intravenously (IV).

63. The method of claim 17 wherein the antibody or fragment thereof is administered sub-cutaneously (SC).

64. The method of claim 17 wherein the antibody or fragment thereof is administered intramuscularly (IM).

65. The method of claim 17 for treating anthrax infection or anthrax toxin poisoning wherein the antibody or fragment thereof is administered in a quantity in the range of 1 to 100 milligrams per kilogram of the animal's body weight.

66. The method of claim 65 wherein the antibody or fragment thereof is administered in a quantity in the range of 1 to 10 milligrams per kilogram of the animal's body weight.

67. The method of claim 17 for treating anthrax infection or anthrax toxin poisoning wherein the antibody or fragment thereof is administered in a quantity in the range of 0.1 to 20 milligrams per kilogram of the animal's body weight.

68. The method of claim 67 wherein the antibody or fragment thereof is administered in a quantity in the range of 1 to 10 milligrams per kilogram of the animal's body weight.

69. The method of claim 17 that prevents or reduces bacteremia associated with anthrax infection.

* * * * *

EXHIBIT B



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Ruben et al.

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(45) Date of Patent: **Oct. 20, 2009**

(54) **ANTIBODIES THAT
IMMUNOSPECIFICALLY BIND TO B
LYMPHOCYTE STIMULATOR PROTEIN**

(75) **Inventors:** Steven M. Ruben, Brookeville, MD
(US); Steven C. Barash, Rockville, MD
(US); Gil H. Choi, Rockville, MD (US);
Tristan Vaughan, Cambridge (GB);
David Hilbert, Bethesda, MD (US)

(73) **Assignee:** Human Genome Sciences, Inc.,
Rockville, MD (US)

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Primary Examiner—Patricia A Duffy

(74) *Attorney, Agent, or Firm*—Leydig, Voit & Mayer, Ltd.

(57) **ABSTRACT**

The present invention relates to antibodies and related mol-
ecules that immunospecifically bind to B Lymphocyte Stimu-
lator. The present invention also relates to methods and com-
positions for detecting or diagnosing a disease or disorder
associated with aberrant B Lymphocyte Stimulator expres-
sion or inappropriate function of B Lymphocyte Stimulator
comprising antibodies or fragments or variants thereof or
related molecules that immunospecifically bind to B Lym-
phocyte Stimulator. The present invention further relates to
methods and compositions for preventing, treating or amelio-
rating a disease or disorder associated with aberrant B Lym-
phocyte Stimulator expression or inappropriate B Lympho-
cyte Stimulator function comprising administering to an
animal an effective amount of one or more antibodies or
fragments or variants thereof or related molecules that immu-
nospecifically bind to B Lymphocyte Stimulator.

25 Claims, 16 Drawing Sheets

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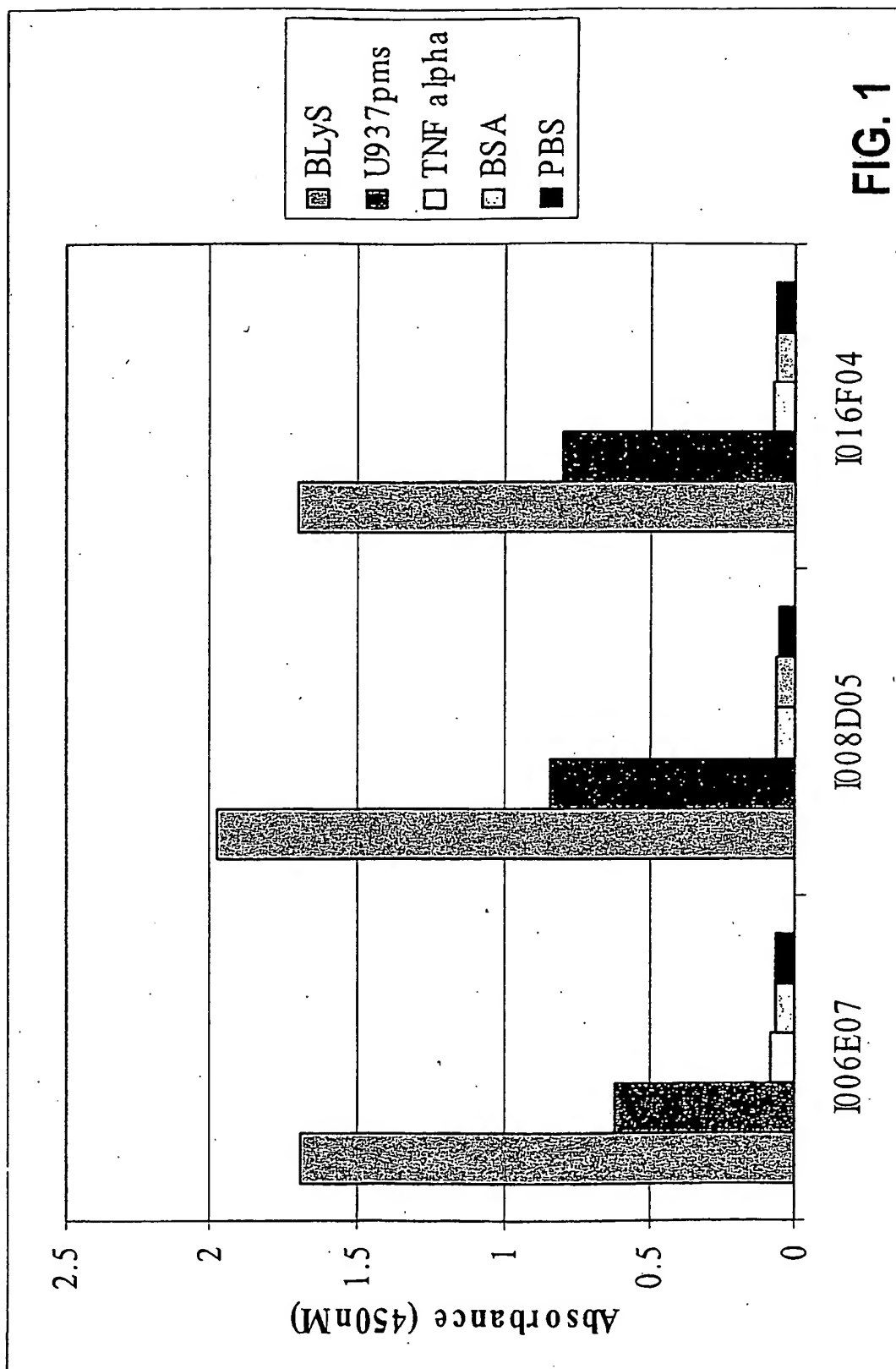
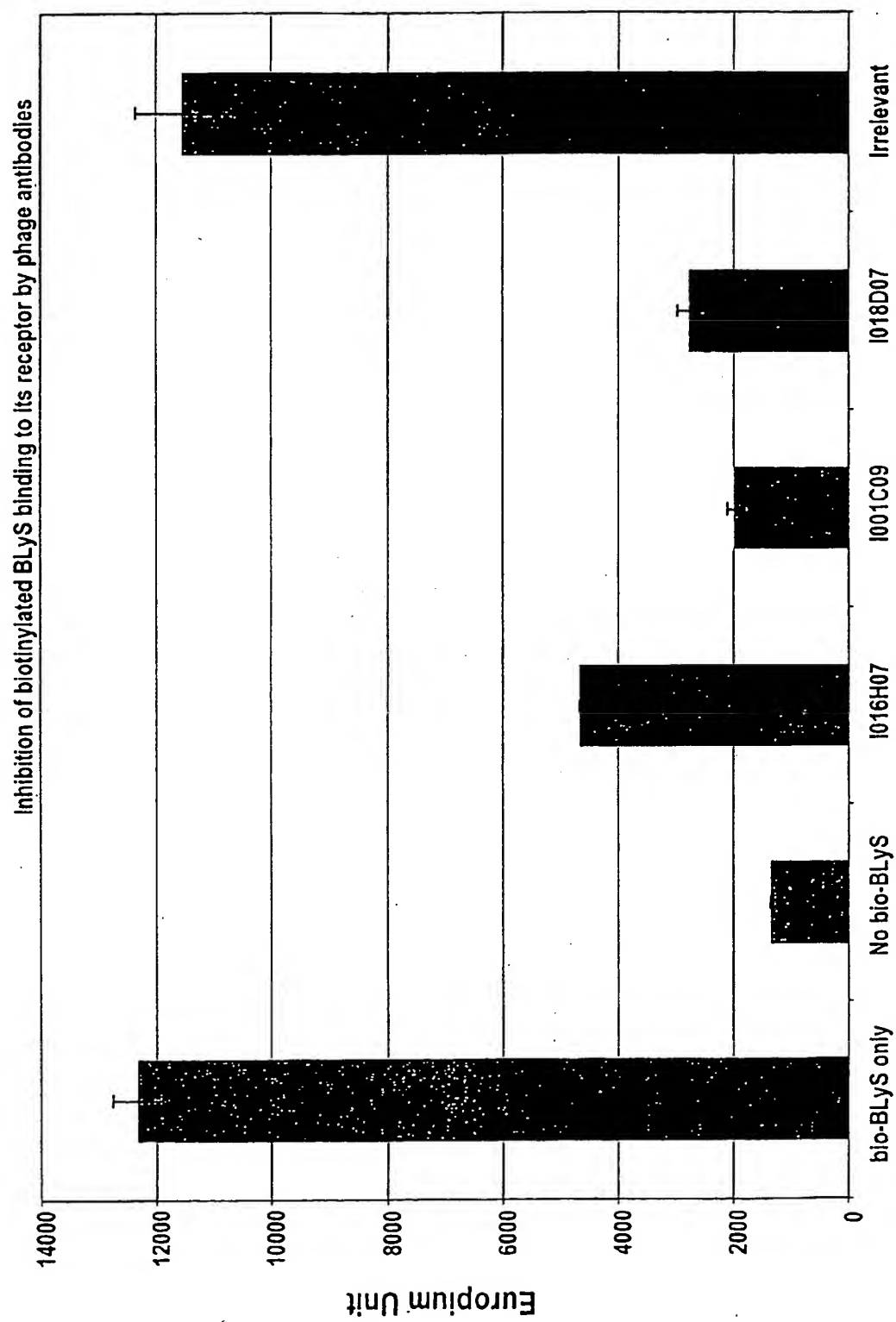


FIG. 2

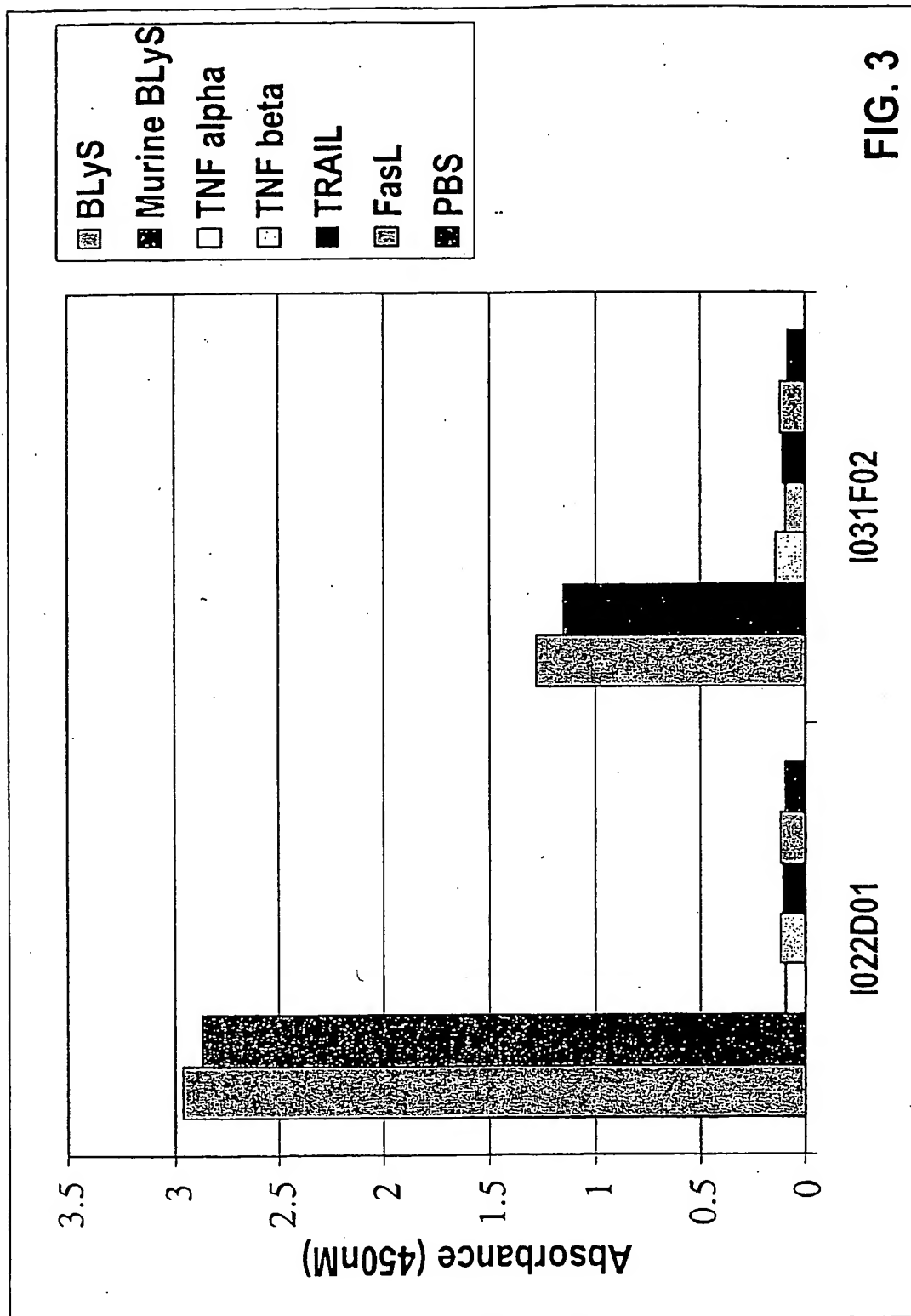
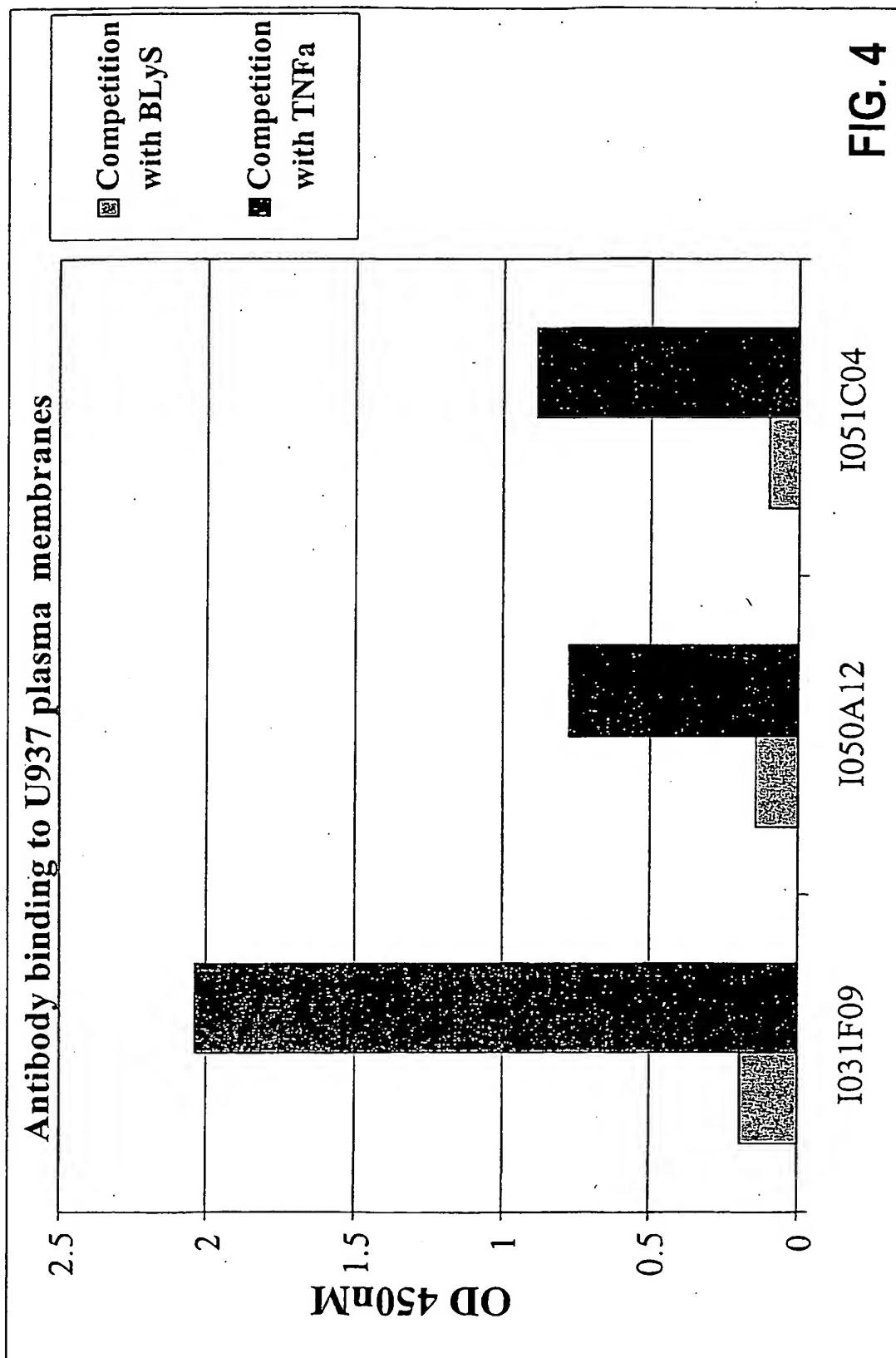
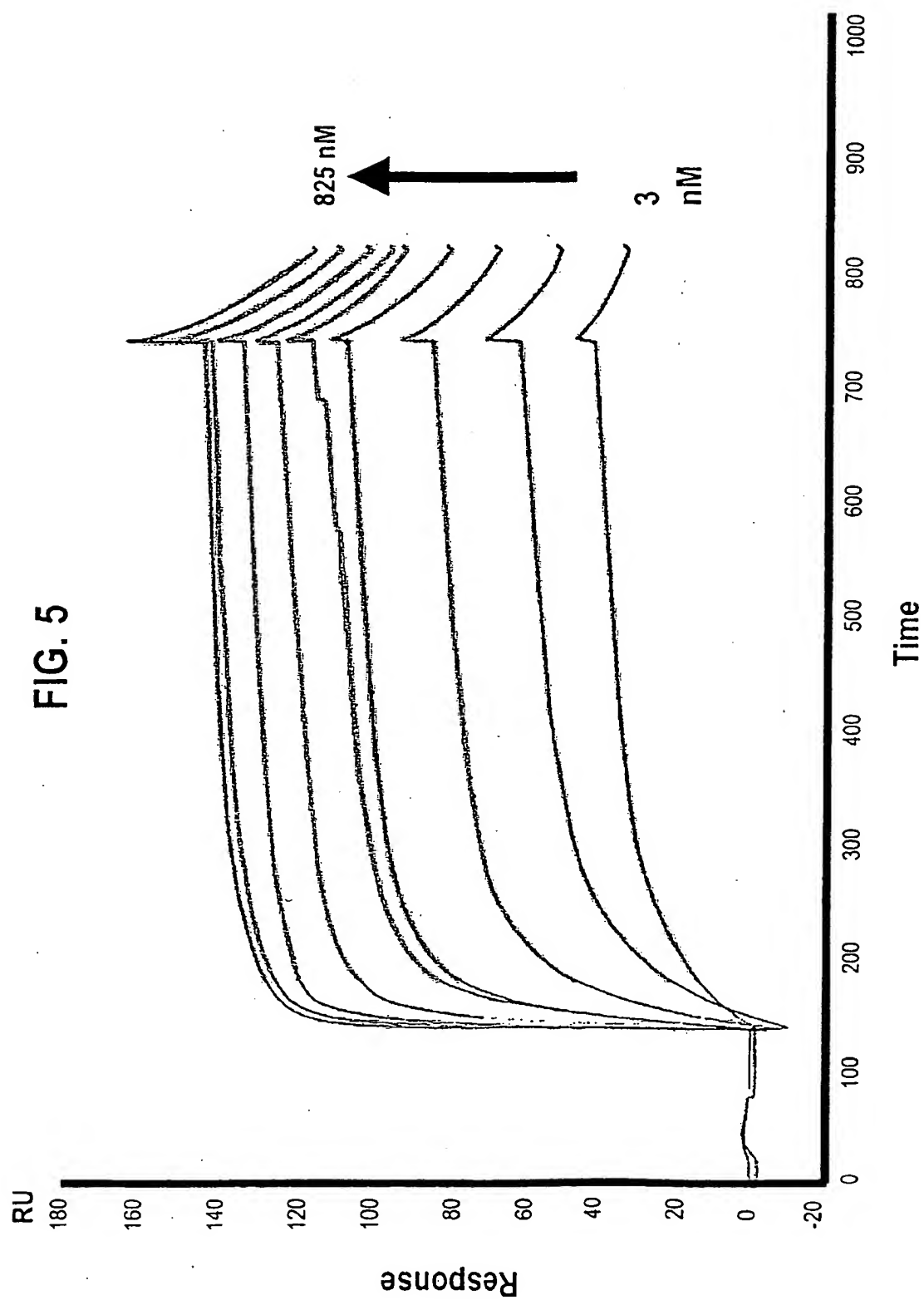
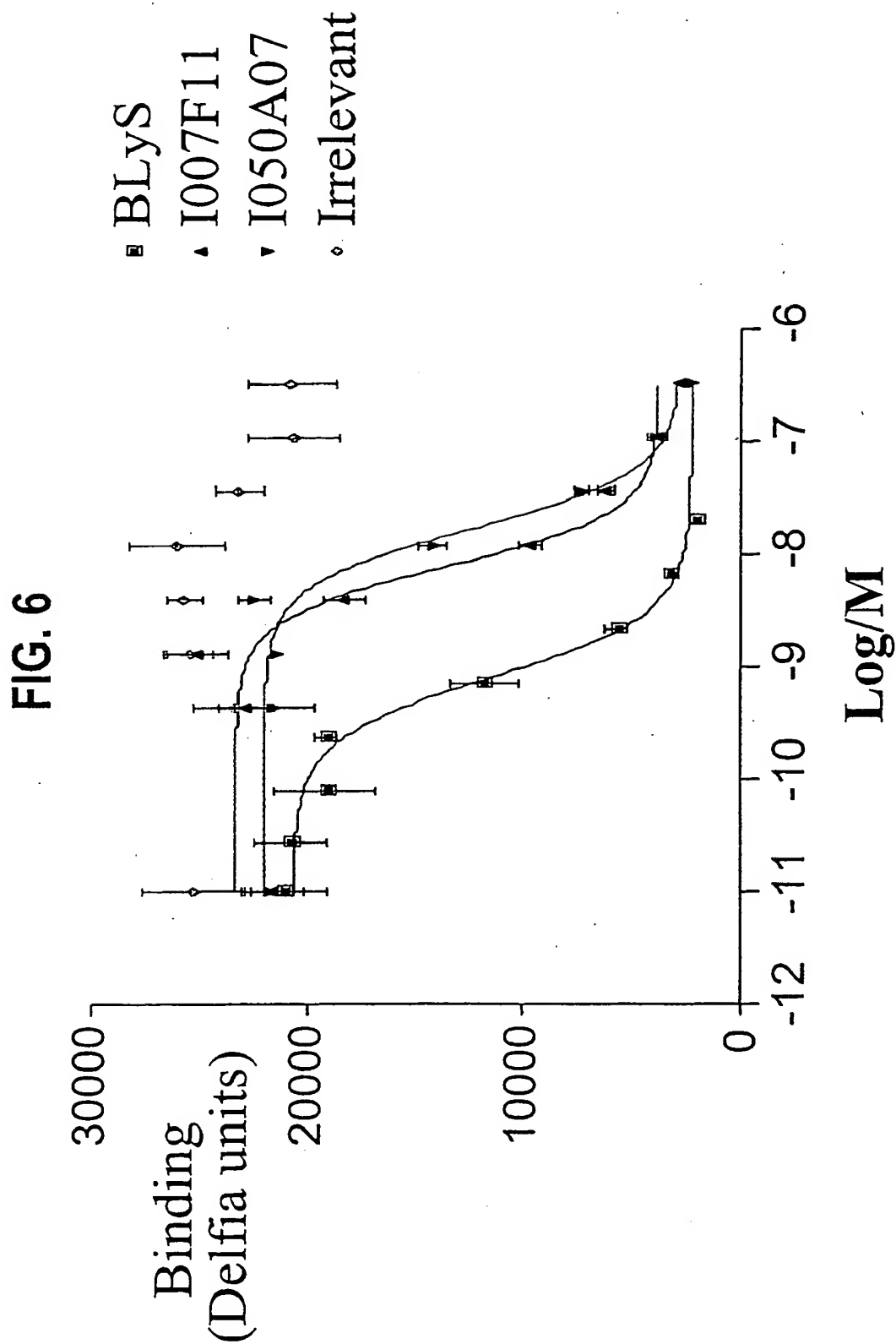


FIG. 3







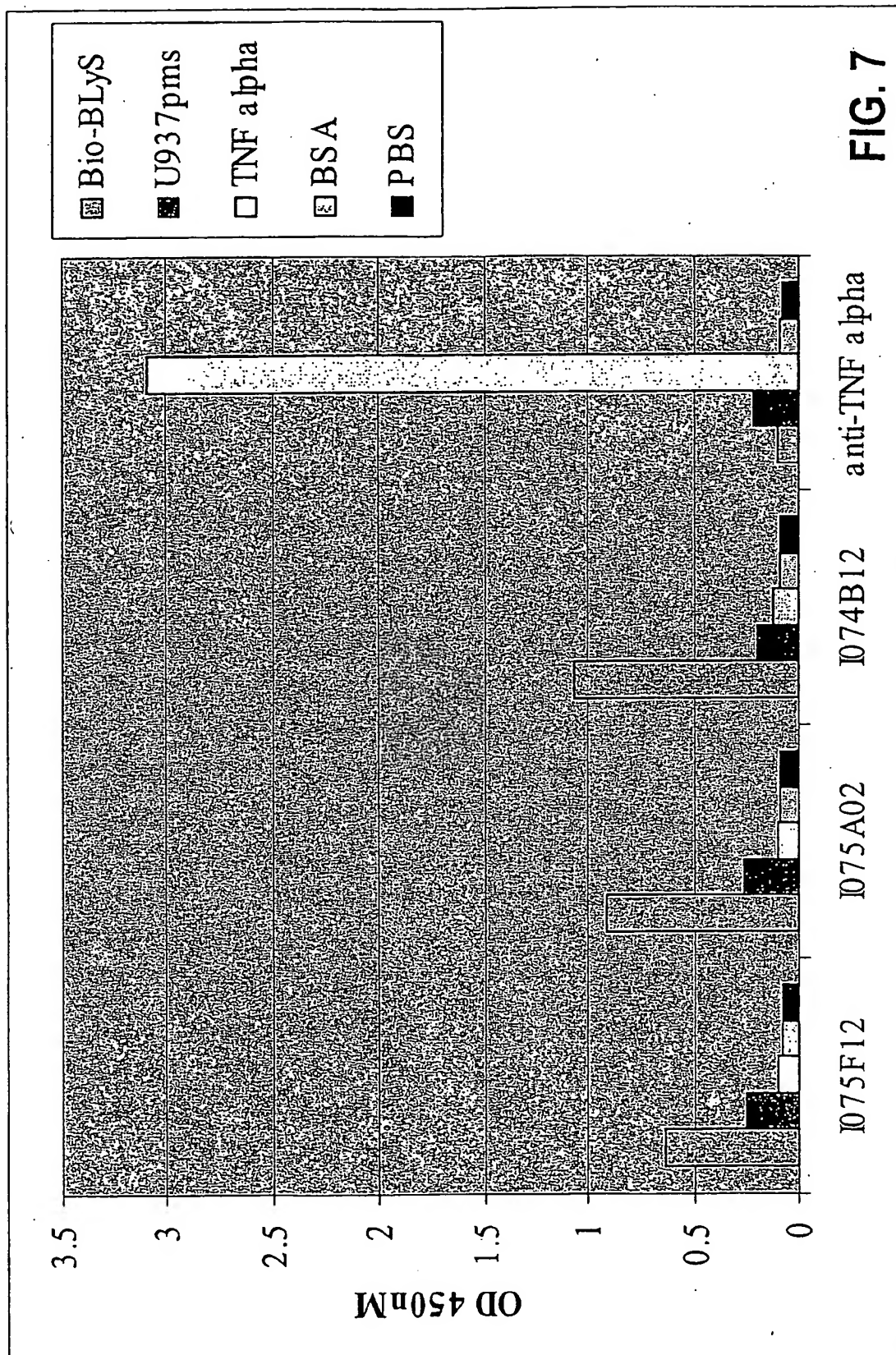
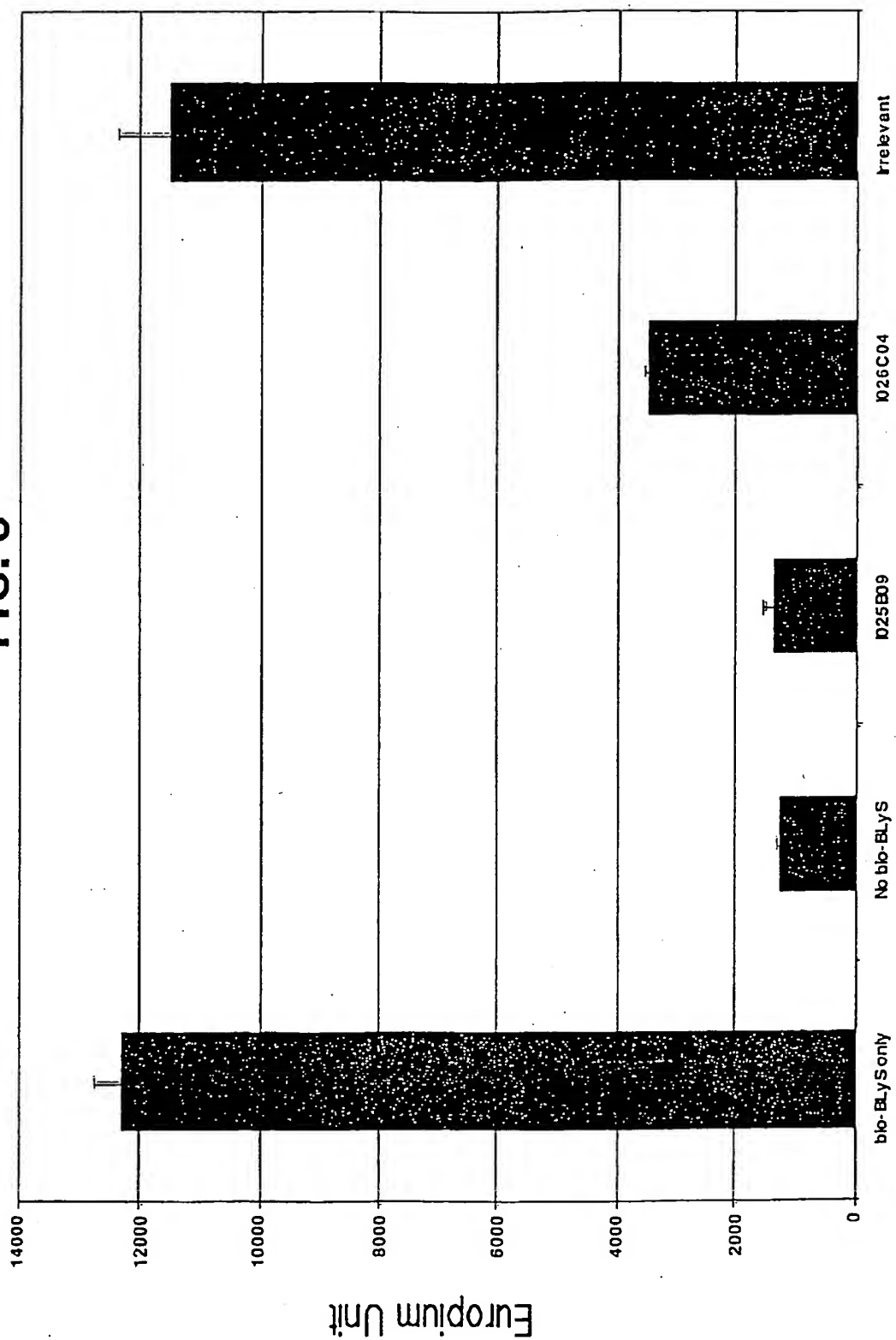
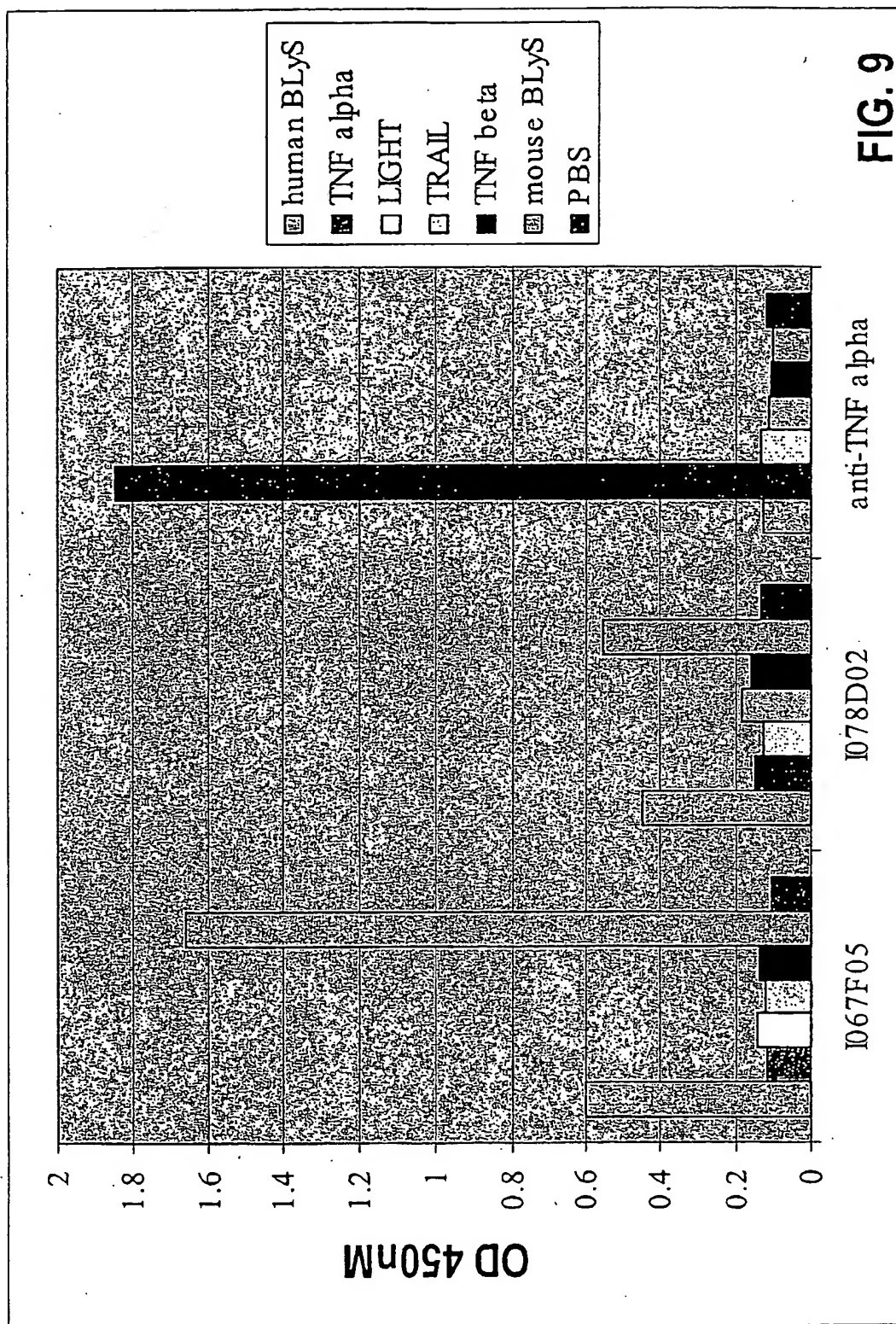


FIG. 8





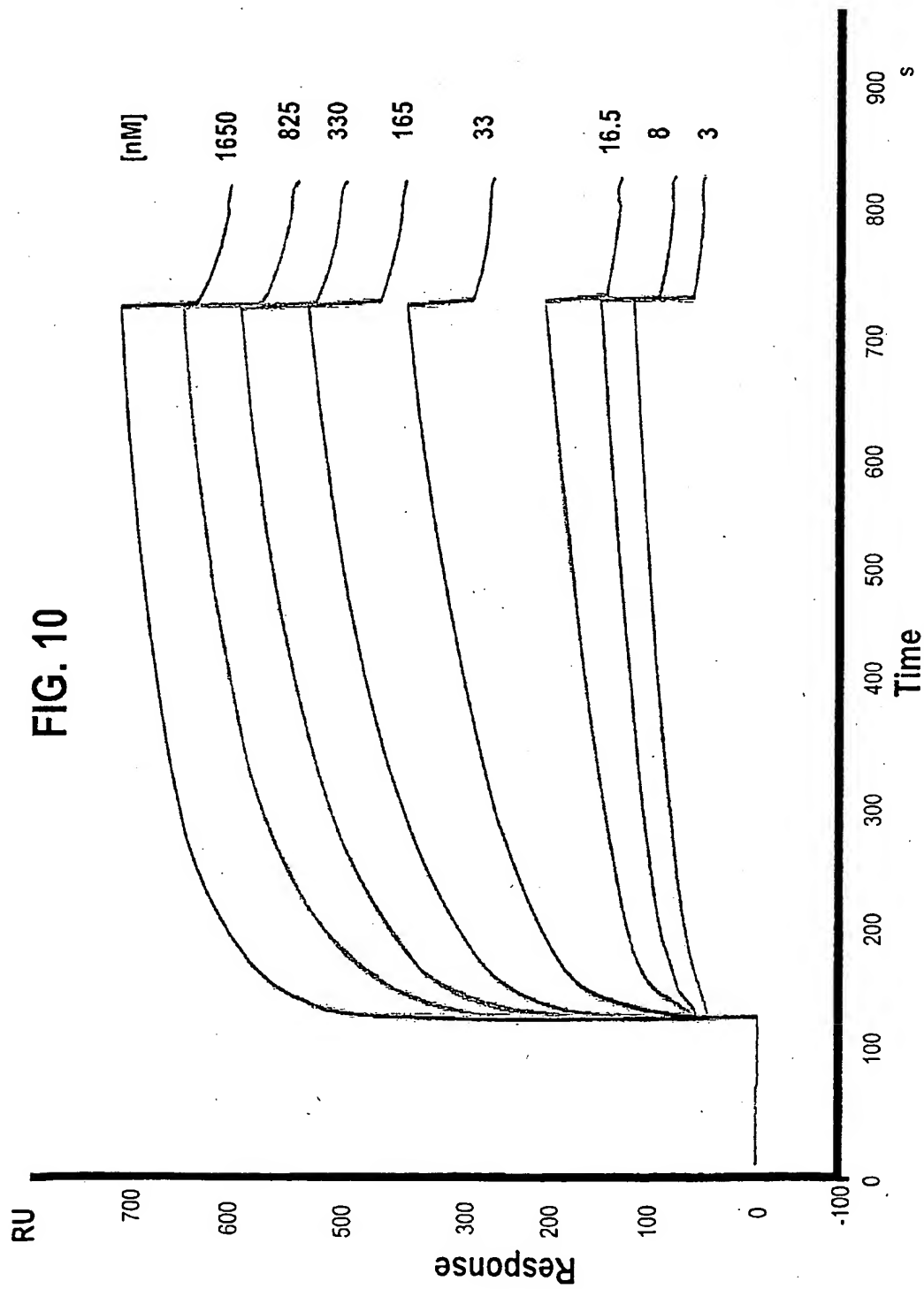
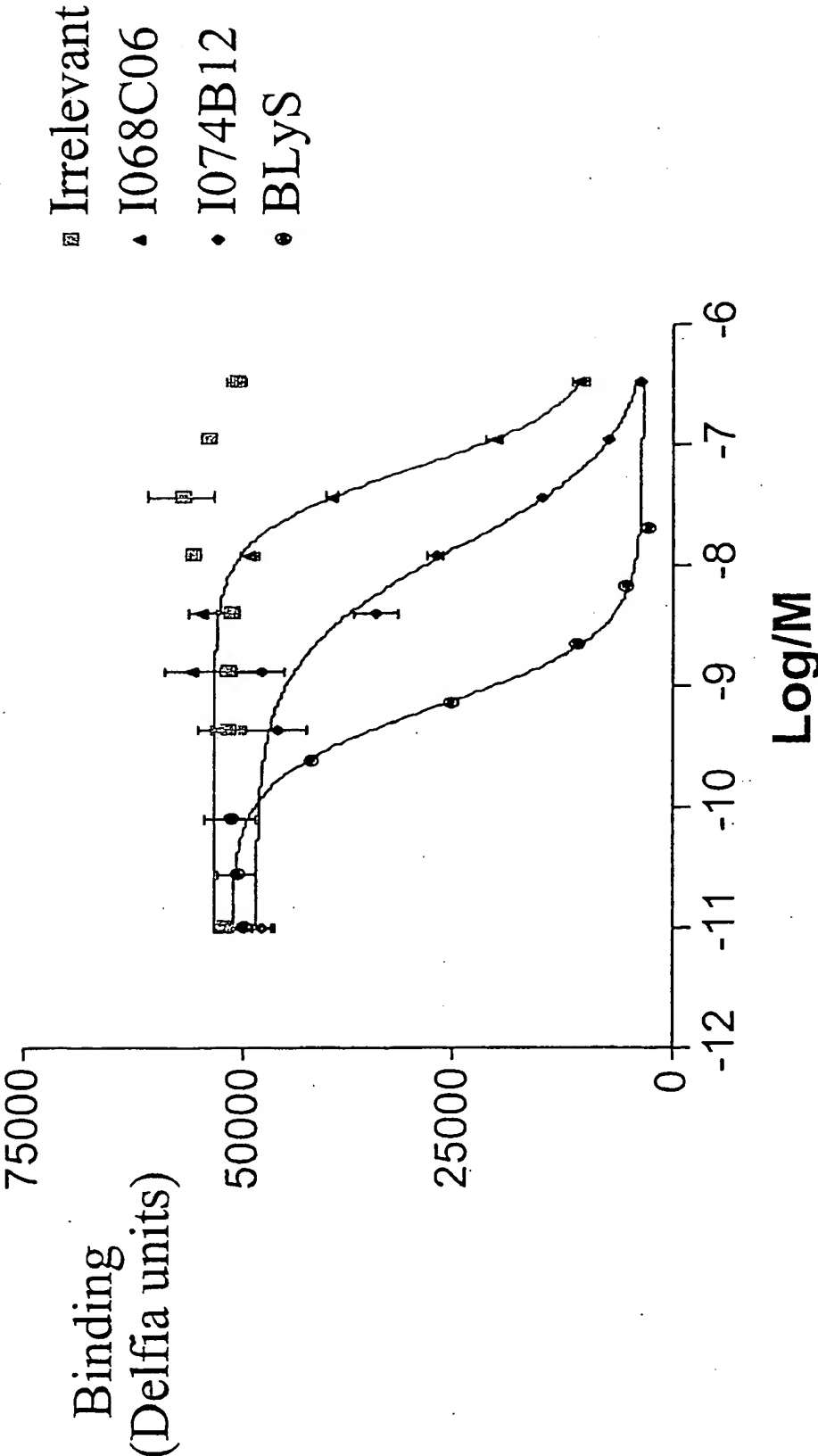


FIG. 11
Scfvs to soluble BLYS only



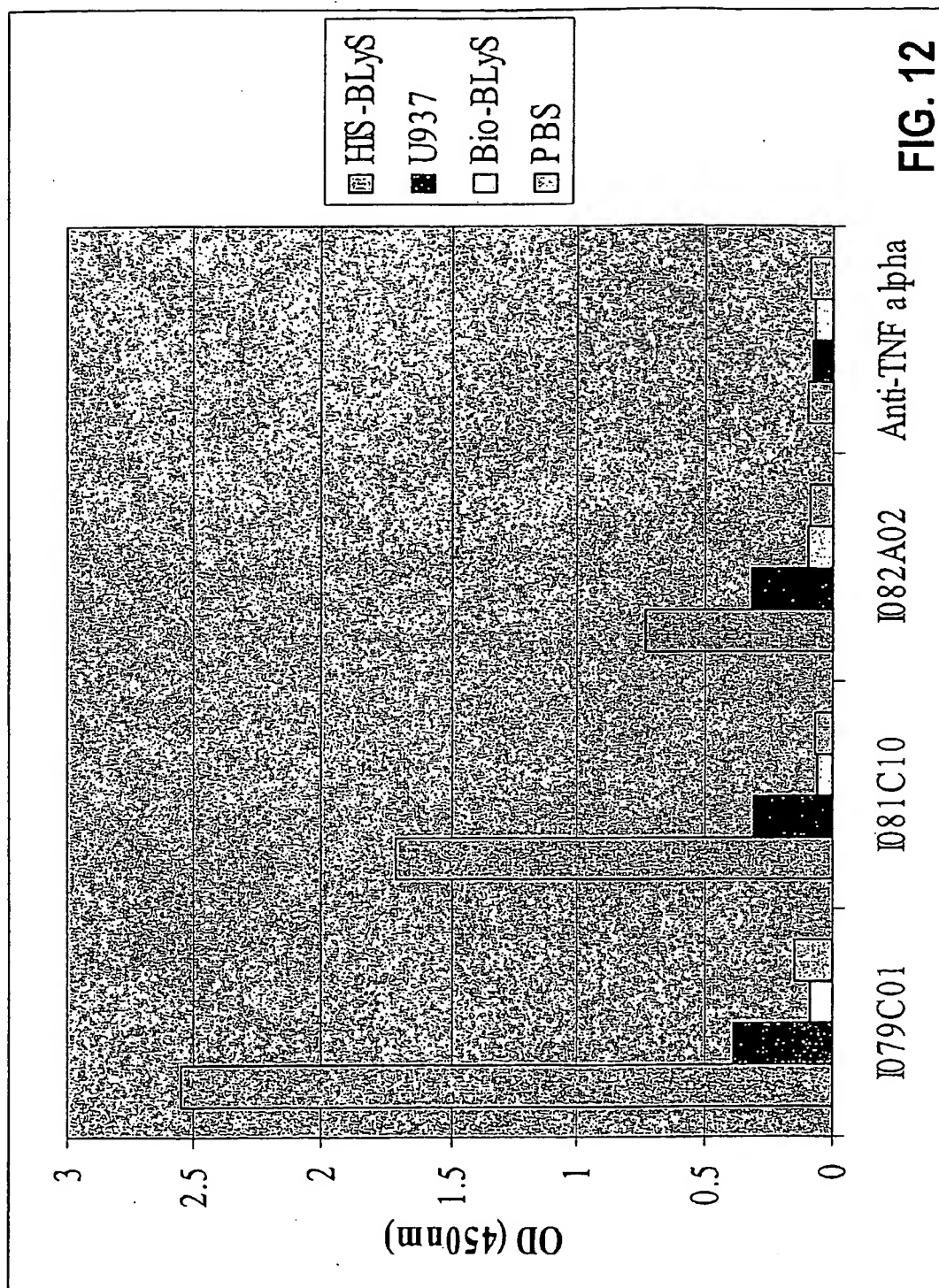


FIG. 12

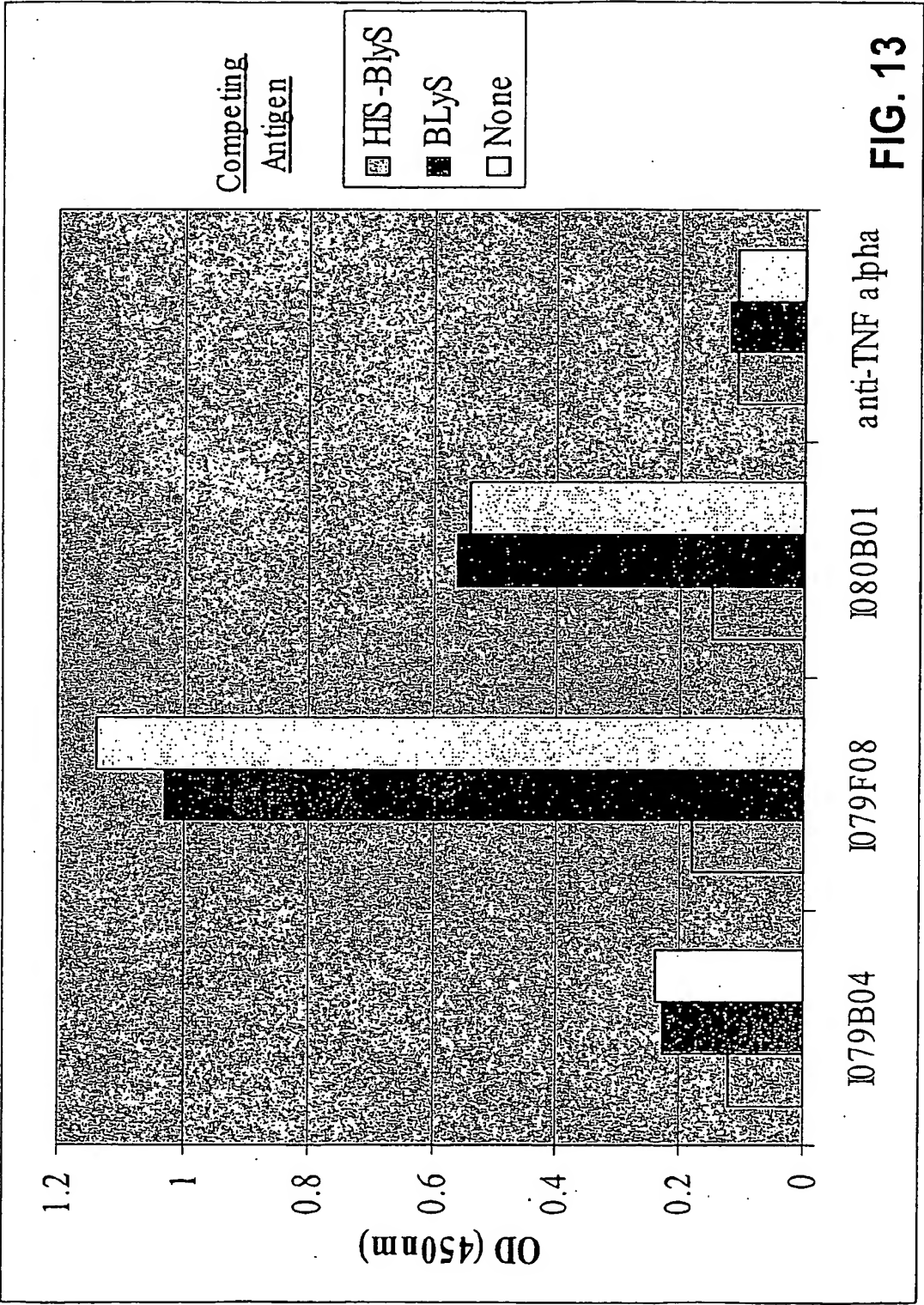


FIG. 14
Plate 1079 Sensorgram - 8 Clones

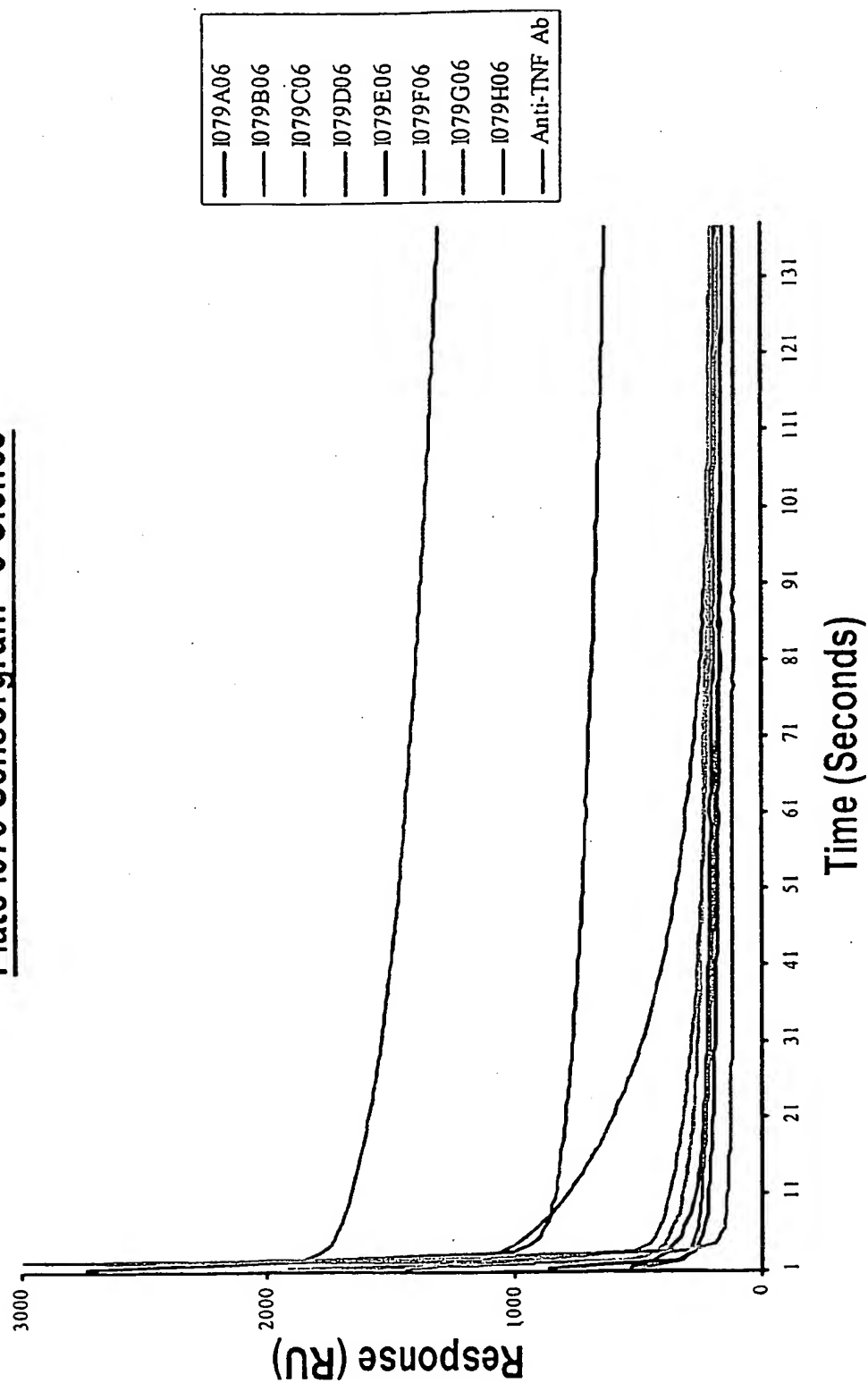
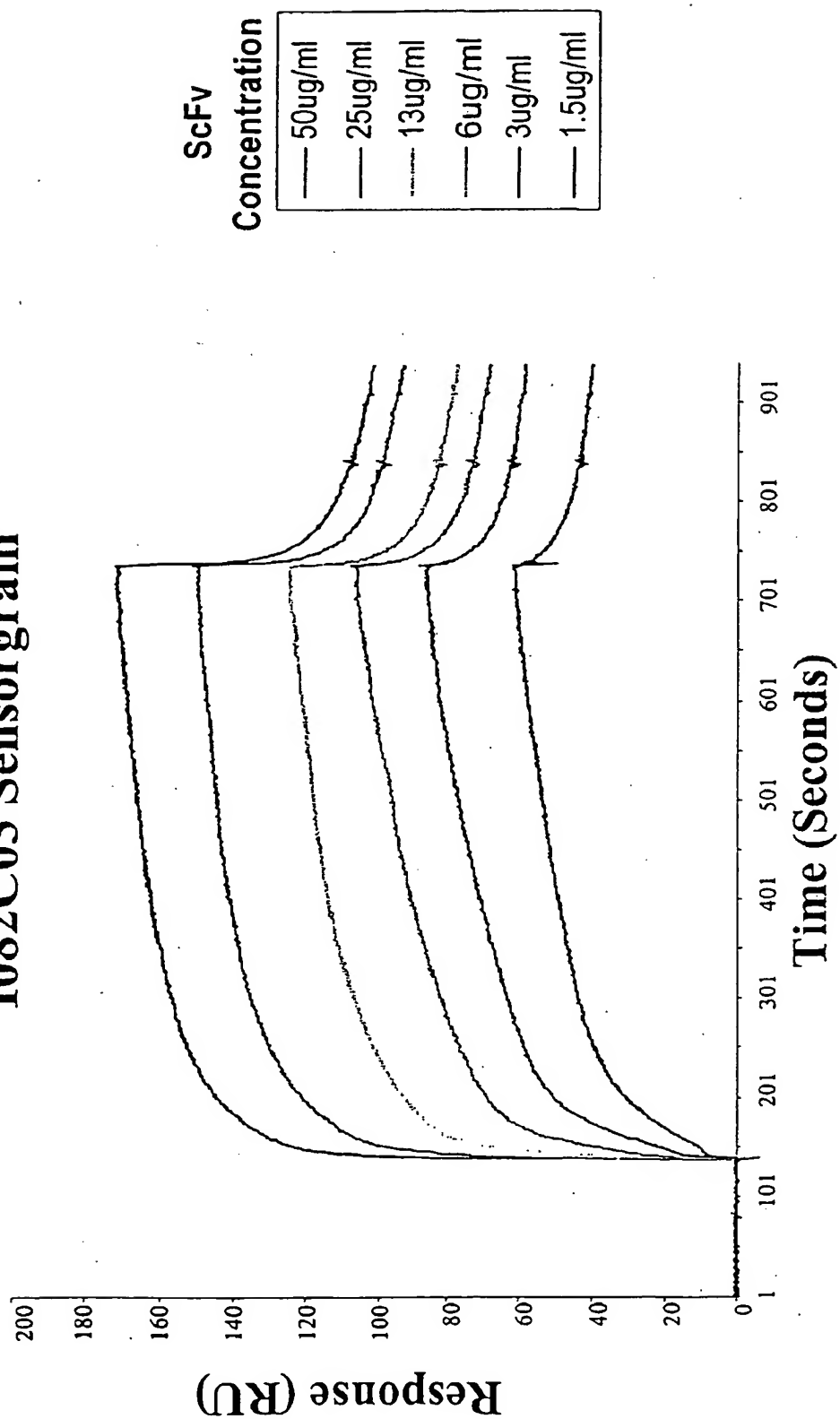
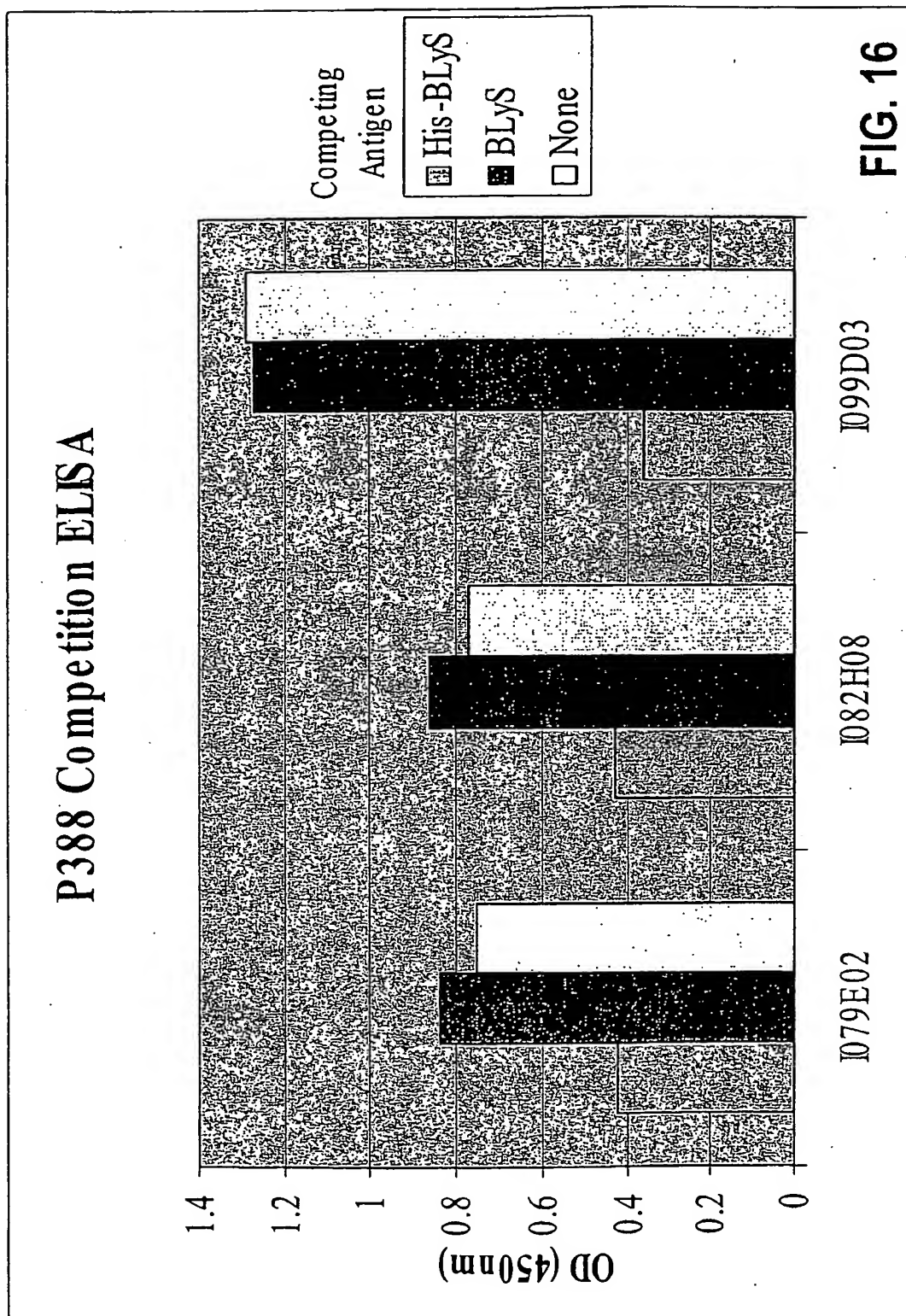


FIG. 15

I082C03 Sensorgram





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ANTIBODIES THAT IMMUNOSPECIFICALLY BIND TO B LYMPHOCYTE STIMULATOR PROTEIN

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a divisional of U.S. application Ser. No. 09/880,748, filed Jun. 15, 2001, which claims benefit of U.S. Provisional Application Nos. 60/212,210, filed Jun. 16, 2000; 60/240,816, filed Oct. 17, 2000; 60/276,248, filed Mar. 16, 2001; 60/277,379, filed Mar. 21, 2001; and 60/293,499, filed May 25, 2001. Each of the above-referenced applications is hereby incorporated by reference herein

STATEMENT UNDER 37 C.F.R. § 1.77(b)(4)

This application refers to a "Sequence Listing" listed below, which is provided as an electronic document on two identical compact discs (CD-R), labeled "Copy 1" and "Copy 2." These compact discs each contain the file "PF523P1D1 Sequence Listing.txt" (4,908,566 bytes, created Nov. 3, 2005), which is hereby incorporated by reference in its entirety. The Sequence Listing may be viewed on an IBM-PC machine running the MS-Windows operating system.

INTRODUCTION

The present invention relates to antibodies and related molecules that immunospecifically bind to B Lymphocyte Stimulator (BLySTM) protein. The present invention also relates to methods and compositions for detecting, diagnosing, or prognosing a disease or disorder associated with aberrant B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor expression or inappropriate function of B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor, comprising antibodies or fragments or variants thereof, or related molecules, that immunospecifically bind to B Lymphocyte Stimulator. The present invention further relates to methods and compositions for preventing, treating or ameliorating a disease or disorder associated with aberrant B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor expression or inappropriate B Lymphocyte Stimulator function or B Lymphocyte Stimulator receptor function, comprising administering to an animal, preferably a human, an effective amount of one or more antibodies or fragments or variants thereof, or related molecules, that immunospecifically bind to B Lymphocyte Stimulator.

BACKGROUND OF THE INVENTION

B Lymphocyte Stimulator (BLySTM) protein is a member of the tumor necrosis factor ("TNF") superfamily that induces both in vivo and in vitro B cell proliferation and differentiation (Moore et al., Science 285: 260-263 (1999)). B Lymphocyte Stimulator is distinguishable from other B cell growth and differentiation factors such as IL-2, IL-4, IL-5, IL-6, IL-7, IL-13, IL-15, CD40L, or CD27L (CD70) by its monocyte-specific gene and protein expression pattern and its specific receptor distribution and biological activity on B lymphocytes. B Lymphocyte Stimulator expression is not detected on natural killer ("NK") cells, T cells or B cells, but is restricted to cells of myeloid origin. B Lymphocyte Stimulator expression on resting monocytes is upregulated by interferon-gamma (IFN-gamma). The gene encoding B Lymphocyte Stimulator has been mapped to chromosome 13q34.

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B Lymphocyte Stimulator is expressed as a 285 amino acid type II membrane-bound polypeptide and a soluble 152 amino acid polypeptide (Moore et al., 1999 supra). The membrane-bound form of B Lymphocyte Stimulator has a predicted transmembrane spanning domain between amino acid residues 47 and 73. The NH₂-terminus of the soluble form of B Lymphocyte Stimulator begins at Ala¹³⁴ of the membrane-bound form of B Lymphocyte Stimulator. Soluble recombinant B Lymphocyte Stimulator has been shown to induce in vitro proliferation of murine splenic B cells and to bind to a cell-surface receptor on these cells (Moore et al., 1999 supra). Soluble B Lymphocyte Stimulator administration to mice has been shown to result in an increase in the proportion of CD45R^{dull}, Ly6D^{bright} (also known as ThB) B cells and an increase in serum IgM and IgA levels (Moore et al., 1999 supra). Thus, B Lymphocyte Stimulator displays a B cell tropism in both its receptor distribution and biological activity.

Based upon its expression pattern and biological activity, B Lymphocyte Stimulator has been suggested to be involved in the exchange of signals between B cells and monocytes or their differentiated progeny. The restricted expression patterns of B Lymphocyte Stimulator receptor and ligand suggest that B Lymphocyte Stimulator may function as a regulator of T cell-independent responses in a manner analogous to that of CD40 and CD40L in T cell-dependent antigen activation. As such, antibodies and related molecules that immunospecifically bind to B Lymphocyte Stimulator may find medical utility in, for example, the treatment of B cell disorders associated with autoimmunity, neoplasia, or immunodeficiency syndromes.

SUMMARY OF THE INVENTION

The present invention encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or polypeptide fragment of B Lymphocyte Stimulator. In particular, the invention encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or polypeptide fragment of human B Lymphocyte Stimulator (SEQ ID NOS: 3228 and/or 3229) or B Lymphocyte Stimulator expressed on human monocytes; murine B Lymphocyte Stimulator (SEQ ID NOS: 3230 and/or 3231) or B Lymphocyte Stimulator expressed on murine monocytes; rat B Lymphocyte Stimulator (either the soluble forms as given in SEQ ID NOS: 3232, 3233, 3234 and/or 3235 or in a membrane associated form, e.g., on the surface of rat monocytes); or monkey B Lymphocyte Stimulator (e.g., the monkey B Lymphocyte Stimulator polypeptides of SEQ ID NOS: 3236 and/or 3237, the soluble form of monkey B Lymphocyte Stimulator, or B Lymphocyte Stimulator expressed on monkey monocytes), preferably human B Lymphocyte Stimulator. The present invention also encompasses methods and compositions for detecting, diagnosing, or prognosing diseases or disorders associated with aberrant B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor expression or inappropriate function of B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor in an animal, preferably a mammal, and most preferably a human, comprising, or alternatively consisting of, use of antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to B Lymphocyte Stimulator. Diseases and disorders which can be detected, diagnosed, or prognosed with the antibodies (including molecules comprising, or alter-

natively consisting of, antibody fragments or variants thereof) of the invention include, but are not limited to, immune disorders (e.g., lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (e.g., asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (e.g., AIDS), and proliferative disorders (e.g., leukemia, carcinoma, and lymphoma). The present invention further encompasses methods and compositions for preventing, treating or ameliorating diseases or disorders associated with aberrant B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor expression or inappropriate function of B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor in an animal, preferably a mammal, and most preferably a human, comprising, or alternatively consisting of, administering to said animal an effective amount of one or more antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to B Lymphocyte Stimulator. Diseases and disorders which can be prevented, treated or ameliorated by administering an effective amount of an antibody of the invention include, but are not limited to, immune disorders (e.g., lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (e.g., asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (e.g., AIDS), and proliferative disorders (e.g., leukemia, carcinoma, and lymphoma).

Using phage display technology, the present inventors have identified single chain antibody molecules ("scFvs") that immunospecifically bind to B Lymphocyte Stimulator, including scFvs that immunospecifically bind to soluble B Lymphocyte Stimulator, scFvs that immunospecifically bind the membrane-bound form of B Lymphocyte Stimulator, and scFvs that immunospecifically bind to both the soluble form and the membrane-bound form of B Lymphocyte Stimulator. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of B Lymphocyte Stimulator, the membrane-bound form of B Lymphocyte Stimulator, and/or both the soluble form and membrane-bound form of B Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules that encode these scFvs, and/or molecules.

In particular, the invention relates to scFvs comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of SEQ ID NOS: 1-2128, preferably SEQ ID NOS: 834-872, 1570-1595, and 1886-1908, and most preferably SEQ ID NOS: 1-46, 321-329, 1563-1569, and 1881-1885, as referred to in Table 1 below. In specific embodiments, the present invention relates to scFvs that immunospecifically bind the soluble form of B Lymphocyte Stimulator, said scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1563-1569, preferably SEQ ID NOS: 1570-1595, and most preferably SEQ ID NOS: 1563-1569, as referred to in Table 1, below. In other embodiments, the present invention also relates to scFvs that immunospecifically bind the membrane-bound form of B Lymphocyte Stimulator, said scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1881-2128, preferably SEQ ID NOS: 1886-1908, and most preferably SEQ ID NOS: 1881-1885, as referred to in Table 1 below. The present invention further relates to scFvs that immunospecifically bind both the membrane-bound form and soluble form of B Lymphocyte Stimulator, said scFvs

comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1-1562, preferably SEQ ID NOS: 834-872, and most preferably SEQ ID NOS: 1-46, and 321-329, as referred to in Table 1 below. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of B Lymphocyte Stimulator, the membrane-bound form of B Lymphocyte Stimulator, and/or both the soluble form and membrane-bound form of B Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules that encode these scFvs, and/or molecules.

The present invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or polypeptide fragment of B Lymphocyte Stimulator, said antibodies comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of any one of the variable heavy ("VH") domains referred to in Table 1, below, or any one of the variable light ("VL") domains referred to in Table 1. In a preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS: 1-46, 321-329, 834-872, 1563-1595, or 1881-1908, as referred to in Table 1 below. In another preferred embodiment, antibodies (including molecules comprising or alternatively consisting of, antibody fragments or variants thereof) of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS: 1-46, 321-329, 834-872, 1563-1595, or 1881-1908, as referred to in Table 1 below. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of B Lymphocyte Stimulator, the membrane-bound form of B Lymphocyte Stimulator, and/or both the soluble form and membrane-bound form of B Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

The present invention also provides antibodies (including molecules comprising or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or a polypeptide fragment of B Lymphocyte Stimulator, said antibodies comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of any one of the VH domains referred to in Table 1, below, and any one of the VL domains referred to in Table 1. In a preferred embodiment, the antibodies of the invention comprise or alternatively consist of, a polypeptide having the amino acid sequence of a VH and VL domain contained in the same scFv referred to in Table 1. In another preferred embodiment, antibodies of the present invention, comprise, or alternatively consist of, a VH domain from an scFv of SEQ ID NOS: 1-46, 321-329, 834-872, 1563-1595, or 1881-1908, as disclosed in Table 1, and a VL domain from an scFv SEQ ID NOS: 1-46, 321-329, 834-872, 1563-1595, or 1881-1908, as disclosed in Table 1. In another preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, the VH and VL domain from a single scFv of SEQ ID NOS: 1-46, 321-329, 834-872, 1563-1595, or 1881-1908, as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH

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domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of B Lymphocyte Stimulator, the membrane-bound form of B Lymphocyte Stimulator, and/or both the soluble form and membrane-bound form of B Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

The present invention also provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or a polypeptide fragment of B Lymphocyte Stimulator, said antibodies comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of any one, two, three or more of the VH complementarity determining regions ("CDRs") (i.e., VH CDR1, VH CDR2, or VH CDR3) referred to in Table 1 and/or any one, two, three or more of the VL CDRs (i.e., VL CDR1, VL CDR2, or VL CDR3) referred to in Table 1. In one embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VH CDR1s referred to in Table 1 and/or any one of the VL CDR1s referred to in Table 1. In another embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VH CDR2s referred to in Table 1 and/or any one of the VL CDR2s referred to in Table 1. In a preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VH CDR3s referred to in Table 1 and/or any one of the VL CDR3s referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of B Lymphocyte Stimulator, the membrane-bound form of B Lymphocyte Stimulator, and/or both the soluble form and membrane-bound form of B Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

In another embodiment, antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) immunospecifically bind to a polypeptide or polypeptide fragment of B Lymphocyte Stimulator, and comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VH CDR1s referred to in Table 1, any one of the VH CDR2s referred to in Table 1, and/or any one of the VH CDR3s referred to in Table 1. In another embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VL CDR1s referred to in Table 1; any one of the VL CDR2s referred to in Table 1, and/or any one of the VL CDR3s referred to in Table 1. In a preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, at least one, two, three, four, five, six, or more CDRs that compound to the same scFv referred to in Table 1, more preferably where CDR1, CDR2, and CDR3 of the VL domain correspond to the same scFv or where CDR1, CDR2, and CDR3 of the VH domain correspond to the same scFv, and most preferably where all six CDRs correspond to the same scFv referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically

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bind the soluble form of B Lymphocyte Stimulator, the membrane-bound form of B Lymphocyte Stimulator, and/or both the soluble form and membrane-bound form of B Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

The present invention also provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that: immunospecifically bind to the soluble form of B Lymphocyte Stimulator (e.g., a polypeptide consisting of amino acids 134-285 of SEQ ID NO:3228); that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator (e.g., a polypeptide consisting of amino acids 1-285 of SEQ ID NO:3228 or a B Lymphocyte Stimulator polypeptide expressed on the surface of monocytes) and/or that immunospecifically bind to both the soluble form and membrane-bound form of B Lymphocyte Stimulator. In a preferred embodiment, antibodies of the present invention immunospecifically bind to the soluble form of B Lymphocyte Stimulator and comprise, or alternatively consist of, a VH domain, VH CDR1, VH CDR2, VH CDR3, VL domain, VL CDR1, VL CDR2, and/or VL CDR3 corresponding to one or more scFvs, that immunospecifically bind to the soluble form of B Lymphocyte Stimulator. In another preferred embodiment, antibodies of the present invention immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator and comprise, or alternatively consist of, a VH domain, VH CDR1, VH CDR2, VH CDR3, VL domain, VL CDR1, VL CDR2, and/or VL CDR3 corresponding to one or more scFvs, that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator. In yet another preferred embodiment, antibodies of the present invention immunospecifically bind to the soluble form and membrane-bound form of B Lymphocyte Stimulator and comprise, or alternatively consist of, a VH domain, VH CDR1, VH CDR2, VH CDR3, VL domain, VL CDR1, VL CDR2, and/or VL CDR3 corresponding to one or more scFvs, that immunospecifically binds to the soluble form and membrane-bound form of B Lymphocyte Stimulator. In another preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, a VH domain and a VL domain corresponding to the same scFv disclosed in Table 1, which antibodies immunospecifically bind to the soluble form of B Lymphocyte Stimulator, the membrane-bound form of B Lymphocyte Stimulator, or both the soluble form and membrane-bound form of B Lymphocyte Stimulator. Nucleic acid molecules encoding these antibodies are also encompassed by the invention. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of B Lymphocyte Stimulator, the membrane-bound form of B Lymphocyte Stimulator, and/or both the soluble form and membrane-bound form of B Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

A VH domain of an amino acid sequence disclosed herein may be combined with a VL domain of an amino acid sequence disclosed herein, or other VL domains, to provide a VH/VL pairing representing an antigen-binding site of an antibody. Similarly, a VL domain of an amino acid sequence disclosed herein may be combined with a VH domain of an amino acid sequence disclosed herein, or other VH domains.

Further, one or more CDRs disclosed herein may be taken from a VH or VL domain and incorporated into a suitable framework as discussed infra.

The present invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof (including derivatives)) comprising, or alternatively consisting of, of VH domains, VL domains and/or CDRs described herein, which antibodies, immunospecifically bind to B Lymphocyte Stimulator (e.g., soluble B Lymphocyte Stimulator and membrane-bound B Lymphocyte Stimulator) and can be routinely assayed for immunospecific binding to B Lymphocyte Stimulator using methods known in the art, such as, for example, the immunoassays disclosed infra. Antibodies and antibody fragments or variants (including derivatives) of the invention may include, for example, one or more amino acid sequence alterations (addition, deletion, substitution and/or insertion of an amino acid residue). These alterations may be made in one or more framework regions and/or one or more CDRs. The antibodies of the invention (including antibody fragments, and variants and derivative thereof) can be routinely made by methods known in the art. Molecules comprising, or alternatively consisting of, fragments or variants of any of the VH domains, VH CDRs; VL domains, and VL CDRs whose sequences are specifically disclosed herein may be employed in accordance with the present invention. Nucleic acid molecules encoding these antibodies and molecules (including fragments, variants, and derivatives) are also encompassed by the invention

The present invention also provides panels of antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants) wherein the panel members correspond to one, two, three, four, five, ten, fifteen, twenty, or more different antibodies of the invention (e.g., whole antibodies, Fabs, F(ab')₂ fragments, Fd fragments, disulfide-linked Fvs (sdFvs), antiidiotypic (anti-Id) antibodies, and scFvs). The present invention further provides mixtures of antibodies, wherein the mixture corresponds to one, two, three, four, five, ten, fifteen, twenty, or more different antibodies of the invention (e.g., whole antibodies, Fabs, F(ab')₂ fragments, Fd fragments, disulfide-linked Fvs (sdFvs), antiidiotypic (anti-Id) antibodies, and scFvs). The present invention also provides for compositions comprising, or alternatively consisting of, one, two, three, four, five, ten, fifteen, twenty, or more antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof). A composition of the invention may comprise, or alternatively consist of, one, two, three, four, five, ten, fifteen, twenty, or more amino acid sequences of one or more antibodies or fragments or variants thereof. Alternatively, a composition of the invention may comprise, or alternatively consist of, nucleic acid molecules encoding one or more antibodies of the invention.

The present invention also provides for fusion proteins comprising an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) of the invention, and a heterologous polypeptide (i.e., a polypeptide unrelated to an antibody or antibody domain). Nucleic acid molecules encoding these fusion proteins are also encompassed by the invention. A composition of the present invention may comprise, or alternatively consist of, one, two, three, four, five, ten, fifteen, twenty or more fusion proteins of the invention. Alternatively, a composition of the invention may comprise, or alternatively consist of, nucleic acid molecules encoding one, two, three, four, five, ten, fifteen, twenty or more fusion proteins of the invention

The present invention also provides for a nucleic acid molecule, generally isolated, encoding an antibody (including molecules such as scFvs, which comprise, or alternatively consist of, an antibody fragment or variant thereof) of the invention. The present invention also provides a host cell transformed with a nucleic acid molecule of the invention and progeny thereof. The present invention also provides a method for the production of an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof) of the invention. The present invention further provides a method of expressing an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof) of the invention from a nucleic acid molecule. These and other aspects of the invention are described in further detail below.

The present invention also encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with aberrant B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor expression or inappropriate B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor function in an animal, preferably a mammal, and most preferably a human, comprising using antibodies (including molecules which comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to B Lymphocyte Stimulator. Diseases and disorders which can be detected, diagnosed or prognosed with the antibodies of the invention include, but are not limited to, immune disorders (e.g., lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (e.g., asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (e.g., AIDS), and proliferative disorders (e.g., leukemia, carcinoma, and lymphoma).

In specific embodiments, the present invention encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with hypergammaglobulinemia (e.g., AIDS, autoimmune diseases, and some immunodeficiencies). In other specific embodiments, the present invention encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with hypogammaglobulinemia (e.g., an immunodeficiency).

The present invention further encompasses methods and compositions for preventing, treating or ameliorating diseases or disorders associated with aberrant B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor expression or inappropriate B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor function in an animal, preferably a mammal, and most preferably a human, comprising administering to said animal an effective amount of one or more antibodies (including molecules which comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to B Lymphocyte Stimulator. Diseases and disorders which can be prevented, treated or inhibited by administering an effective amount of one or more antibodies or molecules of the invention include, but are not limited to, immune disorders (e.g., lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (e.g., asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (e.g., AIDS), and proliferative disorders (e.g., leukemia, carcinoma, and lymphoma).

In specific embodiments, the present invention encompasses methods and compositions (e.g., antagonistic anti-B Lymphocyte Stimulator antibodies) for preventing, treating or ameliorating diseases or disorders associated with hypergammaglobulinemia (e.g., AIDS, autoimmune diseases, and

some immunodeficiency syndromes). In other specific embodiments, the present invention encompasses methods and compositions (e.g., agonistic anti-B Lymphocyte Stimulator antibodies) for preventing, treating or ameliorating diseases or disorders associated with hypogammaglobulinemia (e.g., an immunodeficiency syndrome).

Autoimmune disorders, diseases, or conditions that may be detected, diagnosed, prognosed, or monitored using the antibodies of the invention include, but are not limited to, autoimmune hemolytic anemia, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, autoimmune neutropenia, autoimmune cytopenia, hemolytic anemia, antiphospholipid syndrome, dermatitis, gluten-sensitive enteropathy, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, glomerulonephritis (e.g., IgA nephropathy), Multiple Sclerosis, Neuritis, Uveitis Ophthalmia, Polyendocrinopathies, Purpura (e.g., Henoch-Schoenlein purpura), Reiter's Disease, Stiff-Man Syndrome, Autoimmune Pulmonary Inflammation, myocarditis, IgA glomerulonephritis, dense deposit disease, rheumatic heart disease, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye, autoimmune thyroiditis, hypothyroidism (i.e., Hashimoto's thyroiditis, systemic lupus erythematosus, discoid lupus, Goodpasture's syndrome, Pemphigus, Receptor autoimmune diseases such as, for example, (a) Graves' Disease, (b) Myasthenia Gravis, and (c) insulin resistance, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, rheumatoid arthritis, scleroderma with anti-collagen antibodies, mixed connective tissue disease, polymyositis/dermatomyositis, pernicious anemia, idiopathic Addison's disease, infertility, glomerulonephritis such as primary glomerulonephritis and IgA nephropathy, bullous pemphigoid, Sjögren's syndrome, diabetes mellitus, and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis), chronic active hepatitis, primary biliary cirrhosis, other endocrine gland failure, vitiligo, vasculitis, post-MI, cardiotomy syndrome, urticaria, atopic dermatitis, asthma, inflammatory myopathies, and other inflammatory, granulomatous, degenerative, and atrophic disorders).

Immunodeficiencies that may be detected, diagnosed, prognosed, or monitored using the antibodies of the invention include, but are not limited to, severe combined immunodeficiency (SCID)-X linked, SCID-autosomal, adenosine deaminase deficiency (ADA deficiency), X-linked agammaglobulinemia (XLA), Bruton's disease, congenital agammaglobulinemia, X-linked infantile agammaglobulinemia, acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, transient hypogammaglobulinemia of infancy, unspecified hypogammaglobulinemia, agammaglobulinemia, common variable immunodeficiency (CVID) (acquired), Wiskott-Aldrich Syndrome (WAS), X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, selective IgA deficiency, IgG subclass deficiency (with or without IgA deficiency), antibody deficiency with normal or elevated Igs, immunodeficiency with thymoma, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), selective IgM immunodeficiency, recessive agammaglobulinemia (Swiss type), reticular dysgenesis, neonatal neutropenia, severe congenital leukopenia, thymic aplasia/aplasia or dysplasia with immunodeficiency, ataxia-telangiectasia, short limbed dwarfism, X-linked lymphoproliferative syndrome (XLP), Nezelof syndrome-combined immunodeficiency with Igs, purine nucleo-

side phosphorylase deficiency (PNP), MHC Class II deficiency (Bare Lymphocyte Syndrome) and severe combined immunodeficiency.

Definitions

The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. As such, the term antibody encompasses not only whole antibody molecules, but also antibody fragments as well as variants (including derivatives) of antibodies and antibody fragments. Examples of molecules which are described by the term "antibody" in this application include, but are not limited to: single chain Fvs (scFvs), Fab fragments, Fab' fragments, F(ab')₂, disulfide linked Fvs (sdFvs), Fvs, and fragments comprising or alternatively consisting of, either a VL or a VH domain. The term "single chain Fv" or "scFv" as used herein refers to a polypeptide comprising a VL domain of antibody linked to a VH domain of an antibody. Antibodies that immunospecifically bind to B Lymphocyte Stimulator may have cross-reactivity with other antigens. Preferably, antibodies that immunospecifically bind to B Lymphocyte Stimulator do not cross-react with other antigens. Antibodies that immunospecifically bind to B Lymphocyte Stimulator can be identified, for example, by immunoassays or other techniques known to those of skill in the art, e.g., the immunoassays described in the Examples below.

Antibodies of the invention include, but are not limited to, monoclonal, multispecific, human or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The immunoglobulin molecules of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG₁, IgG₂, IgG₃, IgG₄, IgA₁ and IgA₂) or subclass of immunoglobulin molecule.

Preferably, an antibody of the invention comprises, or alternatively consists of, a VH domain, VH₁ CDR, VL domain, or VL CDR having an amino acid sequence of any one of those referred to in Table 1, or a fragment or variant thereof.

An antibody of the invention "which binds the soluble form of B Lymphocyte Stimulator" is one which binds the 152 amino acid soluble form of the B Lymphocyte Stimulator protein (amino acids 134-285 of SEQ ID NO:3228). In specific embodiments of the invention, an antibody of the invention "which binds the soluble form of B Lymphocyte Stimulator" does not also bind the membrane-bound or membrane-associated form of B Lymphocyte Stimulator. Assays which measure binding to the soluble form of B Lymphocyte Stimulator include, but are not limited to, receptor binding inhibition assay or capture of soluble B Lymphocyte Stimulator from solution as described in Examples 8 and 9.

An antibody of the invention "which binds the membrane-bound form of B Lymphocyte Stimulator" is one which binds the membrane-associated (uncleaved) B Lymphocyte Stimulator protein. In specific embodiments of the invention, an antibody of the invention "which binds the membrane-bound form of B Lymphocyte Stimulator" does not also bind the soluble form of B Lymphocyte Stimulator. Binding to HIS-tagged B Lymphocyte Stimulator (as described herein) in an EUSA is an indicator that an antibody binds the membrane-bound form of B Lymphocyte Stimulator, but should not be relied upon as proof of specificity for the membrane-bound form of B Lymphocyte Stimulator. Assays that may be relied upon as proof of an antibody's specificity for membrane-bound B Lymphocyte Stimulator, include, but are not limited

to, binding to plasma membranes expressing B Lymphocyte Stimulator as described in Example 2. An antibody of the invention "which binds the both the soluble form and the membrane-bound form of B Lymphocyte Stimulator" is one which binds both the membrane-bound form and the soluble form of B Lymphocyte Stimulator.

The term "variant" as used herein refers to a polypeptide that possesses a similar or identical function as a B Lymphocyte Stimulator polypeptide, a fragment of B Lymphocyte Stimulator, an anti-B Lymphocyte Stimulator antibody or antibody fragment thereof, but does not necessarily comprise a similar or identical amino acid sequence of a B Lymphocyte Stimulator polypeptide, a fragment of B Lymphocyte Stimulator, an anti-B Lymphocyte Stimulator antibody or antibody fragment thereof, or possess a similar or identical structure of a B Lymphocyte Stimulator polypeptide, a fragment of B Lymphocyte Stimulator, an anti-B Lymphocyte Stimulator antibody or antibody fragment thereof (including a VH domain, VHCDR, VL domain, or VLCDR having an amino acid sequence of any one of those referred to in Table 1) described herein; (b) a polypeptide encoded by a nucleotide sequence, the complementary sequence of which hybridizes under stringent conditions to a nucleotide sequence encoding a B Lymphocyte Stimulator polypeptide (e.g., SEQ ID NO:3228), a fragment of B Lymphocyte Stimulator, an anti-B Lymphocyte Stimulator antibody or antibody fragment thereof (including a VH domain, VHCDR, VL domain, or VLCDR having an amino acid sequence of any one of those referred to in Table 1), described herein, of at least 5 amino acid residues, at least 10 amino acid residues, at least 15 amino acid residues, at least 20 amino acid residues, at least 25 amino acid residues, at least 30 amino acid residues, at least 40 amino acid residues, at least 50 amino acid residues, at least 60 amino acid residues, at least 70 amino acid residues, at least 80 amino acid residues, at least 90 amino acid residues, at least 100 amino acid residues, at least 125 amino acid residues, or at least 150 amino acid residues; and (c) a polypeptide encoded by a nucleotide sequence that is at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 99%, identical to the nucleotide sequence encoding a B Lymphocyte Stimulator polypeptide, a fragment of B Lymphocyte Stimulator, an anti-B Lymphocyte Stimulator antibody or antibody fragment thereof (including a VH domain, VHCDR, VL domain, or VLCDR having an amino acid sequence of any one of those referred to in Table 1), described herein. A polypeptide with similar structure to a B Lymphocyte Stimulator polypeptide, a fragment of B Lymphocyte Stimulator, an anti-B Lymphocyte Stimulator antibody or antibody fragment thereof, described herein refers to a polypeptide that has a similar secondary, tertiary or quaternary structure of a B Lymphocyte Stimulator polypeptide, a fragment of B Lymphocyte Stimulator, an anti-B Lymphocyte Stimulator antibody, or antibody fragment thereof, described herein. The structure of a polypeptide can be determined by methods known

to those skilled in the art, including but not limited to, X-ray crystallography, nuclear magnetic resonance, and crystallographic electron microscopy.

To determine the percent identity of two amino acid sequences or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino acid or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide at the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., % identity = number of identical overlapping positions / total number of positions × 100%). In one embodiment, the two sequences are the same length.

The determination of percent identity between two sequences can be accomplished using a mathematical algorithm known to those of skill in the art. An example of a mathematical algorithm for comparing two sequences is the algorithm of Karlin and Altschul *Proc. Natl. Acad. Sci. USA* 87:2264-2268(1990), modified as in Karlin and Altschul *Proc. Natl. Acad. Sci. USA* 90:5873-5877(1993). The BLASTn and BLASTx programs of Altschul, et al. *J. Mol. Biol.* 215:403410(1990) have incorporated such an algorithm. BLAST nucleotide searches can be performed with the BLASTn program, score=100, wordlength=12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the BLASTx program, score=50, wordlength=3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al. *Nucleic Acids Res.* 25:3389-3402 (1997). Alternatively, PSI-BLAST can be used to perform an iterated search which detects distant relationships between molecules (Id.). When utilizing BLAST, Gapped BLAST, and PSI-BLAST programs, the default parameters of the respective programs (e.g., BLASTx and BLASTn) can be used. (See www.ncbi.nlm.nih.gov.)

Another example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, *CABIOS* (1989). The ALIGN program (version 2.0) which is part of the GCG sequence alignment software package has incorporated such an algorithm. Other algorithms for sequence analysis known in the art include ADVANCE and ADAM as described in Torellis and Robotti *Comput. Appl. Biosci.* 10:3-5(1994); and FASTA described in Pearson and Lipman *Proc. Natl. Acad. Sci.* 85:2444-8(1988). Within FASTA, ktup is a control option that sets the sensitivity and speed of the search.

The term "derivative" as used herein, refers to a variant polypeptide of the invention that comprises, or alternatively consists of, an amino acid sequence of a B Lymphocyte Stimulator polypeptide, a fragment of B Lymphocyte Stimulator, or an antibody of the invention that immunospecifically binds to B Lymphocyte Stimulator, which has been altered by the introduction of amino acid residue substitutions, deletions or additions. The term "derivative" as used herein also refers to a B Lymphocyte Stimulator polypeptide, a fragment of B Lymphocyte Stimulator, an antibody that immunospecifically binds to B Lymphocyte Stimulator which has been modified, e.g., by the covalent attachment of any type of molecule to the polypeptide. For example, but not by way of limitation, a B

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Lymphocyte Stimulator polypeptide, a fragment of B Lymphocyte Stimulator, or an anti-B Lymphocyte Stimulator antibody, may be modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. A derivative of a B Lymphocyte Stimulator polypeptide, a fragment of B Lymphocyte Stimulator, or an anti-B Lymphocyte Stimulator antibody, may be modified by chemical modifications using techniques known to those of skill in the art, including, but not limited to, specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Further, a derivative of a B Lymphocyte Stimulator polypeptide, a fragment of B Lymphocyte Stimulator, or an anti-B Lymphocyte Stimulator antibody, may contain one or more non-classical amino acids. A polypeptide derivative possesses a similar or identical function as a B Lymphocyte Stimulator polypeptide, a fragment of B Lymphocyte Stimulator, or an anti-B Lymphocyte Stimulator antibody, described herein.

The term "epitopes" as used herein refers to portions of B Lymphocyte Stimulator having antigenic or immunogenic activity in an animal, preferably a mammal. An epitope having immunogenic activity is a portion of B Lymphocyte Stimulator that elicits an antibody response in an animal. An epitope having antigenic activity is a portion of B Lymphocyte Stimulator to which an antibody immunospecifically binds as determined by any method known in the art, for example, by the immunoassays described herein. Antigenic epitopes need not necessarily be immunogenic.

The term "fragment" as used herein refers to a polypeptide comprising an amino acid sequence of at least 5 amino acid residues, at least 10 amino acid residues, at least 15 amino acid residues, at least 20 amino acid residues, at least 25 amino acid residues, at least 30 amino acid residues, at least 35 amino acid residues, at least 40 amino acid residues, at least 45 amino acid residues, at least 50 amino acid residues, at least 10 amino residues, at least 70 amino acid residues, at least 80 amino acid residues, at least 90 amino acid residues, at least 100 amino acid residues, at least 125 amino acid residues, at least 150 amino acid residues, at least 175 amino acid residues, at least 200 amino acid residues, or at least 250 amino acid residues, of the amino acid sequence of B Lymphocyte Stimulator, or an anti-B Lymphocyte Stimulator antibody (including molecules such as scFv's, that comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically B Lymphocyte Stimulator.

The term "fusion protein" as used herein refers to a polypeptide that comprises, or alternatively consists of, an amino acid sequence of an anti-B Lymphocyte Stimulator antibody of the invention and an amino acid sequence of a heterologous polypeptide (i.e. a polypeptide unrelated to an antibody or antibody domain).

The term "host cell" as used herein refers to the particular subject cell transfected with a nucleic acid molecule and the progeny or potential progeny of such a cell. Progeny may not be identical to the parent cell transfected with the nucleic acid molecule due to mutations or environmental influences that may occur in succeeding generations or integration of the nucleic acid molecule into the host cell genome.

DESCRIPTION OF THE FIGURES

FIG. 1. ELISA results for three scFvs, I006E07, I008D05 and I016F04, that immunospecifically bind to U937 membranes, but not to bind to or cross-react with TNF-alpha or BSA.

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FIG. 2. The results for three scFvs, I016H07, I001C09 and I018D07, in a receptor inhibition assay.

FIG. 3. ELISA results for two scFvs (I022D01 and I031F02) demonstrating their ability to bind to human B Lymphocyte Stimulator and to cross-react with mouse B Lymphocyte Stimulator, but not to bind to or cross-react with other antigens of the TNF ligand family.

FIG. 4. ELISA results for three scFvs (I031F09, I050A12, and I051C04) binding to U937 plasma membranes when either B Lymphocyte Stimulator or TNF-alpha is used as a competitor.

FIG. 5. Kinetic analysis of scFv antibody I003C02. A dilution series of I003C02 from 3 nM to 825 nM is shown. Association and dissociation curves were generated using a BIAcore 2000 and BIAevaluation 3.0 software.

FIG. 6. Typical titration curves for two scFv antibodies (I007F11 and I050A07) are shown in FIG. 6. Unlabelled B Lymphocyte Stimulator competed for binding to its receptor with an IC_{50} value of 0.8 nM. The IC_{50} values for I007F11 and I050A07 are 7.9 nM and 17.1 nM, respectively. The assay was performed in triplicate and standard error bars are shown.

FIG. 7. ELISA results for three scFvs clones (I074B12, I075F12 and I075A02) that immunospecifically bind to immobilized B Lymphocyte Stimulator, but not to U937 plasma membranes, TNF-alpha or BSA. As a control, a phage antibody that recognizes TNF α , is also shown in FIG. 7.

FIG. 8. The results for two scFvs (I025B09 and I026C04) in a receptor inhibition assay.

FIG. 9. ELISA results for two scFvs clones (I067F05 and I078D02) demonstrating their ability to bind to immobilized human B Lymphocyte Stimulator and to cross-react with immobilized mouse B Lymphocyte Stimulator, but not to bind to or cross-react with other antigens of the TNF ligand family.

As a control, a phage antibody that recognizes TNF α , is also shown in FIG. 7.

FIG. 10. Kinetic analysis of scFv antibody I002A01. A dilution series of I002A01 from 3 nM to 1650 nM is shown. Association and dissociation curves were generated using a BIAcore 2000 and BIAevaluation 3.0 software.

FIG. 11. Typical titration curves for two scFvs, I0068C06 and I074B12, are shown in FIG. 11. Unlabelled B Lymphocyte Stimulator competed for binding to its receptor with an inhibitory constant 50 (IC_{50}) value of 0.66 nM. The IC_{50} values for I0068C06 and I074B12 are 61 nM and 13 nM, respectively. The assay was performed in triplicate and standard error bars are shown.

FIG. 12. ELISA results for three clones (I079C01, I081C10 and I082A02) demonstrating their ability to bind histidine-tagged B Lymphocyte Stimulator, U937 plasma membranes, but not to bind immobilized biotinylated B Lymphocyte Stimulator.

FIG. 13. ELISA results for three scFvs (I079B04, I079F08, and I080B01) binding to U937 plasma membranes when either histidine-tagged B Lymphocyte Stimulator or biotinylated B Lymphocyte Stimulator is used as a competitor.

FIG. 14. An example of the dissociation section of a typical sensorgram for 8 scFvs is shown in FIG. 14. An anti-TNF α antibody that does not recognize B Lymphocyte Stimulator was included as a control. Of the 8 scFvs exemplified, I079F06 was identified for further study due to the relatively high numbers of RU's bound to the surface.

FIG. 15. A typical example of the binding curves generated for the scFv antibody I082C03 is shown in FIG. 15. The off-rate for this clone was calculated as $2 \times 10^{-3} \text{ s}^{-1}$. The affinity of I082C03 was calculated as 20 nM, assuming 100% activity of the scFv.

FIG. 16. ELISA results for three scFvs (I079B04, I079F08, and I080B01) binding to P388 plasma membranes when either histidine-tagged B Lymphocyte Stimulator or biotinylated B Lymphocyte Stimulator is used as a competitor.

DETAILED DESCRIPTION OF THE INVENTION

The present invention encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to B Lymphocyte Stimulator or a fragment or variant of B Lymphocyte Stimulator. In particular, the invention provides antibodies such as, for example, single chain Fvs (scFvs) having an amino acid sequence of any one of SEQ ID NOS:1-2128, as referred to in Table 1. In particular, the present invention encompasses antibodies that immunospecifically bind to a polypeptide, a polypeptide fragment or variant, or an epitope of human B Lymphocyte Stimulator (SEQ ID NOS:3228 and/or 3229) or B Lymphocyte Stimulator expressed on human monocytes; murine B Lymphocyte Stimulator (SEQ ID NOS:3230 and/or 3231) or B Lymphocyte Stimulator expressed on murine monocytes; rat B Lymphocyte Stimulator (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form, e.g., on the surface of rat monocytes); or monkey B Lymphocyte Stimulator (e.g., the monkey B Lymphocyte Stimulator polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey B Lymphocyte Stimulator, or B Lymphocyte Stimulator expressed on monkey monocytes) (as determined by immunoassays known in the art for assaying specific antibody-antigen binding).

The polypeptide sequence shown in SEQ ID NO:3228 was obtained by sequencing and translating the cDNA of the HNEDU 15 clone which was deposited on Oct. 22, 1996 at the American Type Culture Collection, 10801 University Boulevard, Manassas, Va. 20110-2209, and assigned ATCCTM Accession No. 97768. The deposited clone is contained in the pBluescript SK(-) plasmid (Stratagene, La Jolla, Calif.). The ATCCTM deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

The polypeptide sequence shown in SEQ ID NO:3229 was obtained by sequencing and translating the cDNA of the HDPMC52 clone, which was deposited on Dec. 10, 1998 at the American Type Culture Collection, and assigned ATCCTM Accession No. 203518. The deposited clone is contained in the pBluescript SK(-) plasmid (Stratagene, La Jolla, Calif.). The ATCCTM deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

The B Lymphocyte Stimulator polypeptides bound by the antibodies of the invention may be in monomers or multimers (i.e., dimers, trimers, tetramers and higher multimers). Accordingly, the present invention relates to antibodies that bind monomers and multimers of the B Lymphocyte Stimulator polypeptides of the invention, their preparation, and compositions (preferably, pharmaceutical compositions) containing them. In specific embodiments, the antibodies of the invention bind B Lymphocyte Stimulator monomers, dimers, trimers or tetramers. In additional embodiments, the antibodies of the invention bind at least dimers, at least trimers, or at least tetramers of B Lymphocyte Stimulator.

Multimeric B Lymphocyte Stimulator bound by the antibodies of the invention may be homomers or heteromers. A B Lymphocyte Stimulator homomer, refers to a multimer con-

taining only B Lymphocyte Stimulator polypeptides (including B Lymphocyte Stimulator fragments, variants, and fusion proteins, as described herein). These homomers may contain B Lymphocyte Stimulator polypeptides having identical or different amino acid sequences. In specific embodiments, the antibodies of the invention bind a B Lymphocyte Stimulator homodimer (e.g., containing two B Lymphocyte Stimulator polypeptides having identical or different amino acid sequences) or a B Lymphocyte Stimulator homotrimer (e.g., containing three B Lymphocyte Stimulator polypeptides having identical or different amino acid sequences). In a preferred embodiment, the antibodies of the invention bind homotrimers of B Lymphocyte Stimulator. In additional embodiments, the antibodies of the invention bind a homomeric B Lymphocyte Stimulator multimer which is at least a homodimer, at least a homotrimer, or at least a homotetramer.

Heteromeric B Lymphocyte Stimulator refers to a multimer containing heterologous polypeptides (i.e., polypeptides of a different protein) in addition to the B Lymphocyte Stimulator polypeptides of the invention. In a specific embodiment, the antibodies of the invention bind a B Lymphocyte Stimulator heterodimer, a heterotrimer, or a heterotetramer. In additional embodiments, the antibodies of the invention bind a heteromeric B Lymphocyte Stimulator multimer which is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer. In highly preferred embodiments, the antibodies of the invention bind a heterotrimer comprising both B Lymphocyte Stimulator polypeptides and APRIL polypeptides (SEQ ID NO:3239; GenBank Accession No. AF046888; PCT International Publication Number WO97/33902; J. Exp. Med. 188(6):1185-1190) or fragments or variants thereof. In other highly preferred embodiments, the antibodies of the invention bind a heterotrimer comprising one B Lymphocyte Stimulator polypeptide (including fragments or variants) and two APRIL polypeptides (including fragments or variants). In still other highly preferred embodiments, the antibodies of the invention bind a heterotrimer comprising two B Lymphocyte Stimulator polypeptides (including fragments or variants) and one APRIL polypeptide (including fragments or variants). In a further nonexclusive embodiment, the heteromers bound by the antibodies of the invention contain CD40 ligand polypeptide sequence(s), or biologically active fragment(s) or variant(s) thereof.

In particularly preferred embodiments, the antibodies of the invention bind homomeric, especially homotrimeric, B Lymphocyte Stimulator polypeptides, wherein the individual protein components of the multimers consist of the mature form of B Lymphocyte Stimulator (e.g., amino acids residues 134-285 of SEQ ID NO:3228, or amino acids residues 134-266 of SEQ ID NO:3229) or fragments or variants thereof. In other specific embodiments, antibodies of the invention bind heteromeric, especially heterotrimeric, B Lymphocyte Stimulator polypeptides such as a heterotrimer containing two B Lymphocyte Stimulator polypeptides and one APRIL polypeptide or a heterotrimer containing one B Lymphocyte Stimulator polypeptide and two APRIL polypeptides, and wherein the individual protein components of the B Lymphocyte Stimulator heteromer consist of the mature extracellular soluble portion of either B Lymphocyte Stimulator (e.g., amino acids residues 134-285 of SEQ ID NO:3228, or amino acids residues 134-266 of SEQ ID NO:3229) or fragments or variants thereof, or the mature extracellular soluble portion APRIL (e.g., amino acid residues 105-250 of SEQ ID NO:3239) or fragments or variants thereof.

In specific embodiments, the antibodies of the invention bind conformational epitopes of a B Lymphocyte Stimulator monomeric protein. In specific embodiments, the antibodies

of the invention bind conformational epitopes of a B Lymphocyte Stimulator multimeric, especially trimeric, protein. In other embodiments, antibodies of the invention bind conformational epitopes that arise from the juxtaposition of B Lymphocyte Stimulator with a heterologous polypeptide, such as might be present when B Lymphocyte Stimulator forms heterotrimers (e.g., with APRIL polypeptides (e.g., SEQ ID NO:3239)), or in fusion proteins between B Lymphocyte Stimulator and a heterologous polypeptide.

B Lymphocyte Stimulator multimers bound by the antibodies of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus, in one embodiment, B Lymphocyte Stimulator multimers, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, B Lymphocyte Stimulator heteromultimers, such as, for example, B Lymphocyte Stimulator heterotrimers or B Lymphocyte Stimulator heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, B Lymphocyte Stimulator multimers are formed by covalent associations with and/or between the B Lymphocyte Stimulator polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (e.g., that recited in SEQ ID NO:3228 or SEQ ID NO:3229). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a B Lymphocyte Stimulator fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein (see, e.g., U.S. Pat. No. 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a B Lymphocyte Stimulator-Fc fusion protein. In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another TNF family ligand/receptor member that is capable of forming covalently associated multimers, such as for example, osteoprotegerin (see, e.g., International Publication No. WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from CD40L, or a soluble fragment thereof. In another embodiment, two or B Lymphocyte Stimulator polypeptides are joined through synthetic linkers (e.g., peptide, carbohydrate or soluble polymer linkers). Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple B Lymphocyte Stimulator polypeptides separated by peptide linkers may be produced using conventional recombinant DNA technology.

In one embodiment, antibodies of the invention immunospecifically bind a B Lymphocyte Stimulator polypeptide having the amino acid sequence of SEQ ID NO:3228 or as encoded by the cDNA clone contained in ATCC™ No. 97768, or a polypeptide comprising a portion (i.e., a fragment) of the above polypeptides. In another embodiment, the invention provides an antibody that binds an isolated B Lym-

phocyte Stimulator polypeptide having the amino acid sequence of SEQ ID NO:3229 or the amino acid sequence encoded by the cDNA clone contained in ATCC™ No. 203518, or an antibody that binds polypeptide comprising a portion (i.e., fragment) of the above polypeptides.

Antibodies of the present invention immunospecifically bind to polypeptides comprising or alternatively, consisting of, the amino acid sequence of SEQ ID NO:3228, encoded by the cDNA contained in the plasmid having ATCC™ accession number 97768, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone. Antibodies of the present invention also bind to fragments of the amino acid sequence of SEQ ID NO:3228, encoded by the cDNA contained in the plasmid having ATCC™ accession number 97768, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone.

Additionally, antibodies of the present invention bind polypeptides comprising or alternatively, consisting of, the amino acid sequence of SEQ ID NO:3229, encoded by the cDNA contained in the plasmid having ATCC™ accession number 203518, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone. Antibodies of the present invention also bind to fragments of the amino acid sequence of SEQ ID NO:3229, encoded by the cDNA contained in the plasmid having ATCC™ accession number 203518, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone.

In addition, antibodies of the invention bind polypeptides or polypeptide fragments comprising or alternatively, consisting of, an amino acid sequence contained in SEQ ID NOS: 3230 through 3237.

In specific embodiments, the antibodies of the present invention immunospecifically bind polypeptide fragments including polypeptides comprising or alternatively, consisting of, an amino acid sequence contained in SEQ ID NO:3228, encoded by the cDNA contained in the deposited clone, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone. Protein fragments may be "free standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments that may be bound by the antibodies of the present invention, include, for example, fragments that comprise or alternatively, consist of from about amino acid residues: 1 to 50, 51 to 100, 101 to 150, 151 to 200, 201 to 250, and/or 251 to 285 of SEQ ID NO:3228. Moreover, polypeptide fragments can be at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 175 or 200 amino acids in length.

In specific embodiments, antibodies of the present invention bind polypeptide fragments comprising, or alternatively consisting of, amino acid residues: 1-46, 31-44, 47-72, 73-285, 73-83, 94-102, 148-152, 166-181, 185-209, 210-221, 226-237, 244-249, 253-265, and/or 277-285 of SEQ ID NO:3228.

It will be recognized by one of ordinary skill in the art that mutations targeted to regions of a B Lymphocyte Stimulator polypeptide of SEQ ID NO:3228 which encompass the nineteen amino acid residue insertion which is not found in the B Lymphocyte Stimulator polypeptide sequence of SEQ ID NO:3229 (i.e., amino acid residues Val-142 through Lys-160 of the sequence of SEQ ID NO:3229) may affect the observed

biological activities of the B Lymphocyte Stimulator polypeptide. More specifically, a partial, non-limiting and non-exclusive list of such residues of the B Lymphocyte Stimulator polypeptide sequence which may be targeted for mutation includes the following amino acid residues of the B Lymphocyte Stimulator polypeptide sequence as shown in SEQ ID NO:3228: V-142; T-143; Q-144; D-145; C-146; L-147; Q-148; L-149; I-150; A-151; D-152; S-153; E-154; T-155; P-156; T-157; I-158; Q-159; and K-160. Thus, in specific embodiments, antibodies of the present invention that bind B Lymphocyte Stimulator polypeptides which have one or more mutations in the region from V-142 through K-160 of SEQ ID NO:3228 are contemplated.

Polypeptide fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments that may be bound by antibodies of the present invention, include, for example, fragments that comprise or alternatively, consist of from about amino acid residues: 1 to 15, 16-30, 31-46, 47-55, 56-72, 73-104, 105-163, 163-188, 186-210 and 210-284 of the amino acid sequence disclosed in SEQ ID NO:3228. Additional representative examples of polypeptide fragments that may be bound by antibodies of the present invention, include, for example, fragments that comprise or alternatively, consist of from about amino acid residues: 1 to 143, 1-150, 47-143, 47-150, 73-143, 73-150, 100-150, 140-145, 142-148, 140-150, 140-200, 140-225, and 140-266 of the amino acid sequence disclosed in SEQ ID NO:3229. Moreover, polypeptide fragments that may be bound by antibodies of the present invention, can be at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 175 or 200 amino acids in length. In this context, "about" means the particularly recited ranges and ranges larger or smaller by several, a few, 5, 4, 3, 2 or 1 amino acid residues at either or both the amino- and carboxy-termini.

Additional preferred embodiments encompass antibodies that bind polypeptide fragments comprising, or alternatively consisting of, the predicted intracellular domain of B Lymphocyte Stimulator (e.g., amino acid residues 1-46 of SEQ ID NO:3228), the predicted transmembrane domain of B Lymphocyte Stimulator (e.g., amino acid residues 47-72 of SEQ ID NO:3228), the predicted extracellular domain of B Lymphocyte Stimulator (e.g., amino acid residues 73-285 of SEQ ID NO:3228), the mature soluble extracellular domain of B Lymphocyte Stimulator (e.g., amino acids residues 134-285 of SEQ ID NO:3228), the predicted TNF conserved domain of B Lymphocyte Stimulator (e.g., amino acids 191 to 284 of SEQ ID NO:3228), and a polypeptide comprising, or alternatively, consisting of the predicted intracellular domain fused to the predicted extracellular domain of B Lymphocyte Stimulator (amino acid residues 1-46 fused to amino acid residues 73-285 of SEQ ID NO:3228).

Further additional preferred embodiments encompass polypeptide fragments comprising, or alternatively consisting of, the predicted intracellular domain of B Lymphocyte Stimulator (amino acid residues 1-46 of SEQ ID NO:3229), the predicted transmembrane domain of B Lymphocyte Stimulator (amino acid residues 47-72 of SEQ ID NO:3229), the predicted extracellular domain of B Lymphocyte Stimulator (amino acid residues 73-266 of SEQ ID NO:3229), the predicted TNF conserved domain of B Lymphocyte Stimulator (amino acids 172 to 265 of SEQ ID NO:3229), and a polypeptide comprising, or alternatively, consisting of the predicted intracellular domain fused to the predicted extra-

cellular domain of B Lymphocyte Stimulator (amino acid residues 1-46 fused to amino acid residues 73-266 of SEQ ID NO:3229).

Certain additional embodiments of the invention encompass antibodies that bind polypeptide fragments comprising, or alternatively consisting of, the predicted beta-pleated sheet regions of the B Lymphocyte Stimulator polypeptides of SEQ ID NO:3228 and SEQ ID NO:3229. These polypeptide fragments comprising the beta-pleated sheets of B Lymphocyte Stimulator comprise, or alternatively consist of, amino acid residues Gln-144 to Ala-151, Phe-172 to Lys-173, Ala-177 to Glu-179, Asn-183 to Ile-185, Gly-191 to Lys-204, His-210 to Val-219, Leu-226 to Pro-237, Asn-242 to Ala-251, Gly-256 to Ile-263 and/or Val-276 to Leu-284 of SEQ ID NO:3228. In another, nonexclusive embodiment, these polypeptide fragments comprising the beta-pleated sheets of B Lymphocyte Stimulator comprise, or alternatively consist of, amino acid residues Phe-153 to Lys-154, Ala-158 to Glu-160, Asn-164 to Ile-166, Gly-172 to Lys-185, His-191 to Val-200, Leu-207 to Pro-218, Asn-223 to Ala-232, Gly-237 to Ile-244 and/or Val-257 to Leu-265 of SEQ ID NO:3229.

A partial, non-limiting, and exemplary list of polypeptides that may be bound by the antibodies of the invention includes polypeptides that comprise, or alternatively consist of, combinations of amino acid sequences of the invention includes, for example, [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Val-199 to Ala-248] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228; or [Met-1 to Lys-113] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Val-199 to Ala-248] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228; or [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228. Other combinations of amino acids sequences that may be bound by the antibodies of the invention may include the polypeptide fragments in an order other than that recited above (e.g., [Leu-114 to Thr-141] fused to [Val-199 to Ala-248] fused to [Gly-249 to Leu-285] fused to [Val-142 to Lys-160] of SEQ ID NO:3228). Other combinations of amino acids sequences that may be bound by the antibodies of the invention may also include heterologous polypeptide fragments as described herein and/or other polypeptides or polypeptide fragments of the present invention (e.g., [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228 fused to a FLAG tag; or [Met-1 to Lys-113] of SEQ ID NO:3228 fused to [Leu-114 to Thr-141] of SEQ ID NO:3228 fused to [Glu-135 to Asn-165] of SEQ ID NO:39 fused to [Val-142 to Lys-160] of SEQ ID NO:3228 fused to [Gly-161 to Gln-198] of SEQ ID NO:3228 fused to [Val-199 to Ala-248] of SEQ ID NO:3228 fused to [Gly-249 to Leu-285] of SEQ ID NO:3228).

A partial, non-limiting, and exemplary list of polypeptides that may be bound by the antibodies of the invention includes polypeptides that comprise, or alternatively consist of, combinations of amino acid sequences includes, for example, [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Gly-142 to Gln-179] fused to [Val-180 to Ala-229] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229; [Met-1 to Lys-113] fused to [Gly-142 to Gln-179] fused to [Val-180 to Ala-229] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229; or [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Gly-142 to Gln-179] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229. Other of amino acids sequences that may be bound by the antibodies of the invention combinations may include the polypeptide fragments in an order other than that

recited above (e.g., [Leu-114 to Thr-141] fused to [Val-180 to Ala-229] fused to [Gly-230 to Leu-266] fused to [Gly-142 to Gln-179] of SEQ ID NO:3229). Other combinations of amino acid sequences that may be bound by the antibodies of the invention may also include heterologous polypeptide fragments as described herein and/or other polypeptides or polypeptide fragments of the present invention (e.g., [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Gly-142 to Gln-179] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229 fused to a FLAG tag (SEQ ID NO:3238) or, [Met-1 to Lys-113] of SEQ ID NO:3229 fused to [Leu-114 to Thr-141] of SEQ ID NO:3229 fused to [Glu-135 to Asn-165] of SEQ ID NO:39 fused to [Gly-142 to Gln-179] of SEQ ID NO:3229 fused to [Val-180 to Ala-229] of SEQ ID NO:3229 fused to [Gly-230 to Leu-266] of SEQ ID NO:3229.

Additional embodiments of the invention encompass antibodies that bind B Lymphocyte Stimulator polypeptide fragments comprising, or alternatively consisting of, functional regions of polypeptides of the invention, such as the Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and coil-regions, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Emini surface-forming regions and Jameson-Wolf regions of high antigenic index set out in Tables 9 and 10 and as described herein. In a preferred embodiment, the polypeptide fragments bound by the antibodies of the invention are antigenic (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolff program) of a complete (i.e., full-length) B Lymphocyte Stimulator polypeptide (e.g., SEQ ID NOS:3228 and 3229).

The data representing the structural or functional attributes of the B Lymphocyte Stimulator polypeptide of SEQ ID NO:3228 (Table 9) or the B Lymphocyte Stimulator polypeptide of SEQ ID NO:3229 (Table 10), as described above, was generated using the various modules and algorithms of the DNA*STAR set on default parameters. Column I represents the results of a Garnier-Robson analysis of alpha helical regions; Column II represents the results of a Chou-Fasman analysis of alpha helical regions; Column III represents the results of a Garnier Robson analysis of beta sheet regions;

Column IV represents the results of a Chou-Fasman analysis of beta sheet regions; Column V represents the results of a Garnier Robson analysis of turn regions; Column VI represents the results of a Chou-Fasman analysis of turn regions; Column VII represents the results of a Garnier Robson analysis of coil regions; Column VIII represents a Kyte-Doolittle hydrophilicity plot; Column IX represents a Hopp-Woods hydrophobicity plot; Column X represents the results of an Eisenberg analysis of alpha amphipathic regions; Column XI represents the results of an Eisenberg analysis of beta amphipathic regions; Column XII represents the results of a Karplus-Schultz analysis of flexible regions; Column XIII represents the Jameson-Wolf antigenic index score; and Column XIV represents the Emini surface probability plot.

In a preferred embodiment, the data presented in columns VIII, IX, XIII, and XIV of Tables 9 and 10 can be used to determine regions of the B Lymphocyte Stimulator polypeptide of SEQ ID NO:3228 (Table 9) or the B Lymphocyte Stimulator polypeptide of SEQ ID NO:3229 (Table 10) which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

The above-mentioned preferred regions set out in Tables 9 and 10 include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence set out in SEQ ID NO:2. As set out in Tables 9 and 10, such preferred regions include Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and turn-regions, Kyte-Doolittle hydrophilic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Jameson-Wolf regions of high antigenic index and Emini surface-forming regions. Preferably, antibodies of the present invention bind B Lymphocyte Stimulator polypeptides or B Lymphocyte Stimulator polypeptide fragments and variants comprising regions of B Lymphocyte Stimulator that combine several structural features, such as several (e.g., 1, 2, 3, or 4) of the same or different region features set out above and in Tables 9 and 10.

TABLE 9

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Met	1	A	0.73	-0.71	.	.	.	0.95	1.39
Asp	2	A	T	.	1.12	-0.66	*	.	.	1.15	1.56
Asp	3	A	T	.	1.62	-1.09	*	.	.	1.15	2.12
Ser	4	A	T	.	2.01	-1.51	.	.	.	1.15	4.19
Thr	5	A	T	.	2.40	-2.13	.	.	F	1.30	4.35
Glu	6	A	A	2.70	-1.73	*	*	F	0.90	4.51
Arg	7	A	A	2.81	-1.34	*	*	F	0.90	4.51
Glu	8	A	A	2.00	-1.73	*	*	F	0.90	6.12
Gln	9	A	A	1.99	-1.53	*	*	F	0.90	2.91
Ser	10	A	.	.	B	.	.	.	2.00	-1.04	*	*	F	0.90	2.15
Arg	11	A	.	.	B	.	.	.	1.33	-0.66	*	*	F	0.90	1.66
Leu	12	A	.	.	B	.	.	.	0.41	-0.09	*	*	F	0.45	0.51
Thr	13	A	.	.	B	.	.	.	0.46	0.20	*	*	F	-0.15	0.32
Ser	14	A	A	0.50	-0.19	*	*	.	0.30	0.32
Cys	15	A	A	0.91	-0.19	*	*	.	0.30	0.78
Leu	16	A	A	0.80	-0.87	*	*	F	0.90	1.06
Lys	17	A	A	1.61	-1.36	.	*	F	0.90	1.37
Lys	18	A	A	1.32	-1.74	.	*	F	0.90	4.44
Arg	19	A	A	1.67	-1.70	.	*	F	0.90	5.33
Glu	20	A	A	1.52	-2.39	.	*	F	0.90	5.33
Glu	21	A	A	2.38	-1.70	.	*	F	0.90	2.20
Met	22	A	A	2.33	-1.70	.	*	F	0.90	2.24

TABLE 9-continued

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Lys	23	A	A	1.62	-1.70	*	*	F	0.90	2.24
Leu	24	A	A	0.66	-1.13	*	*	F	0.75	0.69
Lys	25	A	A	0.36	-0.49	.	*	F	0.45	0.52
Glu	26	A	A	.	B	.	.	.	-0.53	-0.71	*	*	.	0.60	0.35
Cys	27	A	A	.	B	.	.	.	-0.74	-0.03	*	*	.	0.30	0.30
Val	28	A	A	.	B	.	.	.	-1.00	-0.03	*	*	.	0.30	0.12
Ser	29	A	A	.	B	.	.	.	-0.08	0.40	*	*	.	-0.30	0.11
Ile	30	A	.	.	B	.	.	.	-0.08	0.40	*	*	.	-0.30	0.40
Leu	31	A	.	.	B	.	.	.	-0.08	-0.17	*	*	.	0.45	1.08
Pro	32	.	.	.	B	.	.	C	0.29	-0.81	*	.	F	1.10	1.39
Arg	33	T	.	.	0.93	-0.81	.	*	F	1.50	2.66
Lys	34	T	.	.	0.93	-1.07	.	.	F	1.84	4.98
Glu	35	C	0.97	-1.37	*	*	F	1.98	4.32
Ser	36	T	C	1.89	-1.16	*	*	F	2.52	1.64
Pro	37	T	C	1.80	-1.16	*	*	F	2.86	1.60
Ser	38	T	T	.	1.39	-0.77	*	.	F	3.40	1.24
Val	39	A	T	.	1.39	-0.39	.	*	F	2.36	1.24
Arg	40	A	1.39	-0.77	*	*	F	2.46	1.60
Ser	41	A	1.34	-1.20	*	*	F	2.46	2.00
Ser	42	T	T	.	1.60	-1.16	.	*	F	3.06	2.67
Lys	43	T	T	.	1.09	-1.80	.	*	F	3.06	2.72
Asp	44	T	T	.	1.13	-1.11	*	*	F	3.40	1.67
Gly	45	A	T	.	0.43	-0.81	*	*	F	2.66	1.03
Lys	46	A	A	0.14	-0.70	.	.	F	1.77	0.52
Leu	47	A	A	0.13	-0.20	*	.	.	0.98	0.31
Leu	48	A	A	-0.72	0.29	*	.	.	0.04	0.46
Ala	49	A	A	-1.53	0.54	.	.	.	-0.60	0.19
Ala	50	A	A	-2.00	1.23	.	.	.	-0.60	0.19
Thr	51	A	A	-2.63	1.23	.	.	.	-0.60	0.19
Leu	52	A	A	-2.63	1.04	.	.	.	-0.60	0.19
Leu	53	A	A	-2.63	1.23	.	.	.	-0.60	0.15
Leu	54	A	A	-2.34	1.41	.	.	.	-0.60	0.09
Ala	55	A	A	-2.42	1.31	.	.	.	-0.60	0.14
Leu	56	A	A	-2.78	1.20	.	.	.	-0.60	0.09
Leu	57	A	T	.	-2.78	1.09	.	.	.	-0.20	0.06
Ser	58	A	T	.	-2.28	1.09	.	.	.	-0.20	0.05
Cys	59	A	T	.	-2.32	1.07	.	.	.	-0.20	0.09
Cys	60	A	T	.	-2.59	1.03	.	.	.	-0.20	0.08
Leu	61	.	.	B	B	.	.	.	-2.08	0.99	.	.	.	-0.60	0.04
Thr	62	.	.	B	B	.	.	.	-1.97	0.99	.	.	.	-0.60	0.11
Val	63	.	.	B	B	.	.	.	-1.91	1.20	.	.	.	-0.60	0.17
Val	64	.	.	B	B	.	.	.	-1.24	1.39	.	.	.	-0.60	0.33
Ser	65	.	.	B	B	.	.	.	-1.43	1.10	.	.	.	-0.60	0.40
Phe	66	A	.	.	B	.	.	.	-1.21	1.26	.	.	.	-0.60	0.40
Tyr	67	A	.	.	B	.	.	.	-1.49	1.11	.	.	.	-0.60	0.54
Gln	68	A	.	.	B	.	.	.	-1.44	0.97	.	.	.	-0.60	0.41
Val	69	A	.	.	B	.	.	.	-0.59	1.27	.	.	.	-0.60	0.39
Ala	70	A	.	.	B	.	.	.	-0.63	0.89	.	.	.	-0.60	0.43
Ala	71	A	.	.	B	.	.	.	0.07	0.56	*	.	.	-0.60	0.25
Leu	72	A	T	.	-0.50	0.16	*	.	.	0.10	0.55
Gln	73	A	T	.	-1.09	0.20	.	.	F	0.25	0.45
Gly	74	A	T	.	-0.53	0.20	.	.	F	0.25	0.45
Asp	75	A	T	.	-0.76	0.09	*	.	F	0.25	0.73
Leu	76	A	A	-0.06	0.09	*	.	F	-0.15	0.35
Ala	77	A	A	0.17	-0.31	*	.	.	0.30	0.69
Ser	78	A	A	0.17	-0.24	*	.	.	0.30	0.42
Leu	79	A	A	-0.30	-0.24	*	.	.	0.30	0.88
Arg	80	A	A	-0.30	-0.24	*	.	.	0.30	0.72
Ala	81	A	A	0.17	-0.34	*	.	.	0.30	0.93
Glu	82	A	A	0.72	-0.30	*	.	.	0.45	1.11
Leu	83	A	A	0.99	-0.49	*	.	.	0.30	0.77
Gln	84	A	A	1.21	0.01	*	.	.	-0.15	1.04
Gly	85	A	A	1.10	0.01	*	.	.	-0.30	0.61
His	86	A	A	1.73	0.01	*	.	.	-0.15	1.27
His	87	A	A	0.92	-0.67	*	.	.	0.75	1.47
Ala	88	A	A	1.52	-0.39	*	.	.	0.45	1.22
Glu	89	A	A	0.93	-0.39	*	.	.	0.45	1.39
Lys	90	A	A	0.93	-0.39	*	.	F	0.60	1.03
Leu	91	A	T	.	0.38	-0.46	*	.	.	0.85	1.01
Pro	92	A	T	.	0.07	-0.46	*	.	.	0.70	0.59
Ala	93	A	T	.	0.07	-0.03	*	.	.	0.70	0.29
Gly	94	A	T	.	-0.14	0.47	.	.	.	-0.20	0.36
Ala	95	A	-0.14	0.21	.	.	.	-0.10	0.36
Gly	96	A	0.08	-0.21	.	.	F	0.65	0.71
Ala	97	A	-0.06	-0.21	.	.	F	0.65	0.72
Pro	98	A	-0.28	-0.21	.	.	F	0.65	0.71
Lys	99	A	A	0.07	-0.03	.	.	F	0.45	0.59

TABLE 9-continued

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Ala	100	A	A	0.66	-0.46	.	.	F	0.60	1.01
Gly	101	A	A	0.41	-0.96	.	.	F	0.90	1.13
Leu	102	A	A	0.79	-0.89	.	.	F	0.75	0.57
Glu	103	A	A	0.41	-0.46	*	.	F	0.45	0.88
Glu	104	A	A	-0.49	-0.46	*	.	F	0.45	0.89
Ala	105	A	A	-0.21	-0.24	.	.	.	0.30	0.81
Pro	106	A	A	-0.46	-0.44	.	.	.	0.30	0.67
Ala	107	A	A	0.01	0.06	.	.	.	-0.30	0.39
Val	108	A	A	-0.80	0.49	.	*	.	-0.60	0.38
Thr	109	A	A	-0.76	0.67	.	*	.	-0.60	0.20
Ala	110	A	A	-1.06	0.24	.	*	.	-0.30	0.40
Gly	111	A	A	-1.54	0.43	*	*	.	-0.60	0.38
Leu	112	A	A	-0.96	0.57	*	*	.	-0.60	0.23
Lys	113	.	A	B	-0.31	0.09	*	*	.	-0.30	0.39
Ile	114	.	A	B	-0.21	0.01	*	*	.	-0.30	0.61
Phe	115	.	A	B	-0.21	0.01	*	*	.	0.15	1.15
Glu	116	.	A	C	-0.08	-0.17	*	.	F	1.25	0.58
Pro	117	.	A	C	0.39	0.26	*	*	F	1.10	1.28
Pro	118	C	0.34	-0.00	.	.	F	2.20	1.47
Ala	119	T	C	0.89	-0.79	.	*	F	3.00	1.47
Pro	120	T	C	1.59	-0.36	.	*	F	2.25	0.94
Gly	121	T	T	.	1.29	-0.39	.	*	F	2.15	0.98
Glu	122	T	T	.	1.20	-0.43	.	.	F	2.00	1.30
Gly	123	C	1.41	-0.54	.	.	F	1.60	1.12
Asn	124	T	C	2.00	-0.57	.	.	F	1.50	1.97
Ser	125	T	C	1.91	-0.60	.	*	F	1.50	1.82
Ser	126	T	C	2.37	-0.21	.	*	F	1.54	2.47
Gln	127	T	C	2.37	-0.64	.	*	F	2.18	3.01
Asn	128	C	2.76	-0.64	.	.	F	2.32	3.61
Ser	129	T	C	2.87	-1.03	.	.	F	2.86	5.39
Arg	130	T	T	.	2.58	-1.41	*	.	F	3.40	6.09
Asn	131	T	T	.	2.02	-1.31	*	.	F	3.06	3.83
Lys	132	T	T	.	2.02	-1.07	*	.	F	2.72	2.12
Arg	133	T	.	.	1.68	-1.06	*	.	F	2.18	1.88
Ala	134	C	1.77	-0.63	*	.	F	1.64	1.15
Val	135	C	1.66	-0.60	*	.	F	1.49	0.89
Gln	136	C	1.66	-0.60	*	.	F	1.83	0.79
Gly	137	T	C	1.30	-0.60	*	.	F	2.52	1.35
Pro	138	T	C	0.33	-0.61	*	.	F	2.86	2.63
Glu	139	T	T	.	0.61	-0.61	*	.	F	3.40	1.13
Glu	140	A	T	.	1.47	-0.53	*	.	F	2.66	1.64
Thr	141	A	1.47	-0.56	.	.	F	2.12	1.84
Val	142	A	1.14	-0.99	.	.	F	1.78	1.77
Thr	143	A	T	.	0.54	-0.41	.	.	F	1.19	0.55
Gln	144	A	T	.	0.54	0.27	*	.	F	0.25	0.31
Asp	145	A	T	.	-0.27	0.19	*	.	F	0.25	0.73
Cys	146	A	T	.	-0.84	0.23	*	.	.	0.10	0.42
Leu	147	A	A	-0.58	0.43	*	.	.	-0.60	0.17
Gln	148	A	A	-0.27	0.53	*	.	.	-0.60	0.10
Leu	149	A	A	-0.57	0.53	*	*	.	-0.30	0.32
Ile	150	A	A	-0.57	0.34	*	.	.	0.30	0.52
Ala	151	.	A	C	-0.21	-0.34	.	*	.	1.40	0.52
Asp	152	T	T	.	0.39	-0.26	.	*	F	2.45	0.91
Ser	153	T	C	0.08	-0.51	.	.	F	3.00	2.00
Glu	154	T	C	-0.00	-0.71	.	.	F	2.70	2.86
Thr	155	T	C	0.89	-0.53	*	.	F	2.40	1.20
Pro	156	.	.	.	B	.	.	C	1.52	-0.13	*	.	F	1.56	1.55
Thr	157	.	.	.	B	T	.	.	1.18	-0.51	*	.	F	1.92	1.79
Ile	158	A	.	.	B	.	.	.	1.18	-0.09	.	.	F	1.08	1.23
Gln	159	T	T	.	0.93	-0.19	.	.	F	2.04	1.07
Lys	160	T	T	.	0.93	0.14	*	.	F	1.60	1.16
Gly	161	T	T	.	0.44	0.14	*	.	F	1.44	2.38
Ser	162	T	T	.	-0.10	0.24	*	.	F	1.28	1.19
Tyr	163	.	.	.	B	T	.	.	0.58	0.49	*	.	.	0.12	0.44
Thr	164	.	.	B	B	.	.	.	0.29	0.91	*	.	.	-0.44	0.69
Phe	165	.	.	B	B	.	.	.	-0.57	1.40	*	.	.	-0.60	0.54
Val	166	.	.	B	B	.	.	.	-1.03	1.70	.	.	.	-0.60	0.29
Pro	167	.	.	B	B	.	.	.	-1.03	1.63	.	.	.	-0.60	0.16
Trp	168	A	.	.	B	.	.	.	-1.49	1.53	.	*	.	-0.60	0.25
Leu	169	A	.	.	B	.	.	.	-1.13	1.53	*	.	.	-0.60	0.29
Leu	170	A	.	.	B	.	.	.	-0.32	0.89	*	.	.	-0.30	0.38
Ter	171	A	0.19	0.46	*	.	.	0.20	0.71
Phe	172	T	.	.	0.10	-0.03	*	.	.	1.80	0.85
Lys	173	T	T	.	-0.20	-0.33	*	.	F	2.60	1.38
Arg	174	T	C	-0.20	-0.51	.	.	F	3.00	1.04
Gly	175	T	C	0.61	-0.21	.	.	F	2.25	0.99
Ser	176	A	T	.	0.91	-1.00	*	.	F	2.05	0.86

TABLE 9-continued

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Ala	177	A	A	1.66	-1.00	*	.	F	1.35	0.76
Leu	178	A	A	1.61	-1.00	.	.	F	1.20	1.54
Glu	179	A	A	1.50	-1.43	.	.	F	0.90	1.98
Glu	180	A	A	1.89	-1.41	*	.	F	0.90	3.16
Lys	181	A	A	1.30	-1.91	*	.	F	0.90	7.66
Glu	182	A	A	1.08	-1.91	.	.	F	0.90	3.10
Asn	183	A	A	1.03	-1.23	*	*	F	0.90	1.48
Lys	184	A	A	1.08	-0.59	*	.	F	0.75	0.55
Ile	185	A	A	1.08	-0.59	*	*	.	0.60	0.63
Leu	186	A	A	0.72	-0.59	*	*	.	0.60	0.68
Val	187	A	A	0.38	-0.50	.	.	.	0.30	0.49
Lys	188	A	A	0.13	-0.07	*	*	F	0.45	0.69
Glu	189	A	T	.	-0.61	0.00	*	*	F	0.40	1.32
Thr	190	T	T	.	-0.42	0.10	.	*	F	0.80	1.54
Gly	191	T	T	.	-0.50	0.24	*	.	F	0.65	0.67
Tyr	192	T	T	.	0.11	0.93	*	*	.	0.20	0.27
Phe	193	.	.	B	B	.	.	.	-0.28	1.69	.	.	.	-0.60	0.29
Phe	194	.	.	B	B	.	.	.	-0.28	1.63	.	*	.	-0.60	0.29
Ile	195	.	.	B	B	.	.	.	-0.82	1.60	.	.	.	-0.60	0.32
Tyr	196	.	.	B	B	.	.	.	-1.29	1.49	.	.	.	-0.60	0.28
Gly	197	.	.	.	B	T	.	.	-1.29	1.39	.	.	.	-0.20	0.26
Gln	198	.	.	.	B	T	.	.	-0.90	1.36	.	.	.	-0.20	0.59
Val	199	.	.	.	B	.	.	C	-0.20	1.16	.	.	.	-0.40	0.54
Leu	200	.	.	.	B	.	.	C	0.73	0.40	.	.	.	-0.10	0.92
Tyr	201	T	T	.	0.67	-0.03	.	.	.	1.25	1.06
Thr	202	T	T	.	0.77	0.06	.	.	F	0.80	2.06
Asp	203	T	T	.	0.18	0.17	.	.	F	0.80	3.91
Lys	204	A	T	.	0.43	-0.01	.	.	F	1.00	2.52
Thr	205	A	A	0.90	-0.16	.	.	F	0.60	1.73
Tyr	206	A	A	1.11	-0.21	.	.	.	0.45	1.03
Ala	207	A	A	0.61	0.29	.	.	.	-0.30	0.70
Met	208	A	A	-0.28	0.97	.	.	.	-0.60	0.40
Gly	209	A	A	.	B	.	.	.	-0.32	1.17	*	.	.	-0.60	0.18
His	210	A	A	.	B	.	.	.	0.10	0.81	*	.	.	-0.60	0.31
Leu	211	A	A	.	B	.	.	.	0.39	0.31	.	.	.	-0.30	0.61
Ile	212	A	A	.	B	.	.	.	1.02	-0.30	.	.	.	0.45	1.22
Gln	213	A	A	.	B	.	.	.	0.77	-0.73	.	*	.	0.75	1.80
Arg	214	A	A	.	B	.	.	.	1.08	-0.59	.	*	F	0.90	1.62
Lys	215	A	A	.	B	.	.	.	0.26	-0.77	*	*	F	0.90	3.14
Lys	216	A	A	.	B	.	.	.	0.37	-0.81	.	*	F	0.90	1.35
Val	217	.	A	B	B	.	.	.	0.91	-0.43	*	*	.	0.30	0.60
His	218	.	A	B	B	.	.	.	0.91	-0.00	.	*	.	0.30	0.29
Val	219	.	A	B	B	.	.	.	0.80	-0.00	*	*	.	0.30	0.25
Phe	220	.	.	B	B	.	.	.	-0.06	-0.00	*	.	.	0.30	0.57
Gly	221	A	.	.	B	.	.	.	-0.40	0.04	.	*	.	-0.30	0.35
Asp	222	A	-0.36	-0.07	*	.	.	0.50	0.63
Glu	223	A	-1.18	-0.03	*	.	.	0.50	0.60
Leu	224	A	.	.	B	.	.	.	-0.63	-0.17	.	.	.	0.30	0.45
Ser	225	A	.	.	B	.	.	.	-0.74	-0.11	.	.	.	0.30	0.39
Leu	226	A	.	.	B	.	.	.	-1.10	0.57	.	*	.	-0.60	0.18
Val	227	A	.	.	B	.	.	.	-0.99	1.36	.	*	.	-0.60	0.19
Thr	228	A	.	.	B	.	.	.	-1.66	0.67	*	*	.	-0.60	0.28
Leu	229	A	.	.	B	.	.	.	-1.73	0.86	*	.	.	-0.60	0.18
Phe	230	A	.	.	B	.	.	.	-1.43	0.86	*	.	.	-0.60	0.17
Arg	231	A	.	.	B	.	.	.	-0.62	0.61	*	.	.	-0.60	0.21
Cys	232	.	.	.	B	T	.	.	-0.37	0.53	*	.	.	-0.20	0.41
Ile	233	.	.	.	B	T	.	.	-0.27	0.46	*	.	.	-0.20	0.46
Gln	234	.	.	.	B	T	.	.	0.54	0.10	*	.	.	0.10	0.37
Asn	235	.	.	.	B	.	.	C	0.93	0.10	*	.	.	0.05	1.19
Met	236	.	.	.	B	.	.	C	0.01	0.01	*	.	F	0.20	2.44
Pro	237	.	.	.	B	.	.	C	0.47	0.01	*	.	F	0.44	1.16
Glu	238	T	.	.	1.36	0.04	*	.	F	1.08	1.12
Thr	239	C	1.36	0.04	*	.	F	1.12	1.82
Leu	240	C	1.06	-0.17	*	.	F	1.96	1.89
Pro	241	T	.	.	0.99	-0.21	.	.	F	2.40	1.46
Asn	242	T	.	.	0.96	0.36	.	.	F	1.41	0.54
Asn	243	T	T	.	0.66	0.63	.	.	F	1.22	1.03
Ser	244	T	T	.	0.38	0.33	.	.	F	1.13	0.89
Cys	245	T	T	.	0.84	0.40	.	.	.	0.74	0.56
Tyr	246	T	T	.	0.17	0.43	.	.	.	0.20	0.35
Ser	247	A	-0.42	0.71	.	.	.	-0.40	0.18
Ala	248	A	A	-0.38	0.83	.	.	.	-0.60	0.34
Gly	249	A	A	-0.89	0.26	.	.	.	-0.30	0.43
Ile	250	A	A	-0.22	0.19	*	.	.	-0.30	0.27
Ala	251	A	A	0.02	-0.20	*	.	.	0.30	0.46
Lys	252	A	A	-0.02	-0.70	.	.	.	0.60	0.80
Leu	253	A	A	0.57	-0.70	.	.	F	0.90	1.13

TABLE 9-continued

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Glu	254	A	A	0.91	-1.39	.	.	F	0.90	1.87
Glu	255	A	A	0.99	-1.89	.	.	F	0.90	1.62
Gly	256	A	A	1.58	-1.20	.	*	F	0.90	1.62
Asp	257	A	A	0.72	-1.49	.	*	F	0.90	1.62
Glu	258	A	A	0.94	-0.80	*	*	F	0.75	0.77
Leu	259	A	A	0.06	-0.30	*	*	.	0.30	0.79
Gln	260	A	A	-0.16	-0.04	*	.	.	0.30	0.33
Leu	261	A	A	0.30	0.39	*	.	.	-0.30	0.30
Ala	262	A	A	0.30	0.39	*	.	.	-0.30	0.70
Ile	263	A	A	0.30	-0.30	.	*	.	0.30	0.70
Pro	264	A	T	.	0.52	-0.30	.	*	F	1.00	1.37
Arg	265	A	T	.	0.52	-0.49	.	*	F	1.00	1.37
Glu	266	A	T	.	0.44	-0.59	*	*	F	1.30	3.38
Asn	267	A	T	.	0.73	-0.59	*	*	F	1.30	1.53
Ala	268	A	0.81	-0.63	*	*	.	0.95	1.05
Gln	269	A	1.02	0.06	*	.	.	-0.10	0.50
Ile	270	A	0.57	0.06	.	*	.	0.15	0.52
Ser	271	C	0.57	0.09	.	*	.	0.60	0.51
Leu	272	C	-0.29	-0.41	.	*	F	1.60	0.49
Asp	273	T	T	.	-0.01	-0.17	.	*	F	2.25	0.52
Gly	274	T	T	.	-0.71	-0.37	.	*	F	2.50	0.56
Asp	275	T	T	.	-0.52	0.03	.	*	F	1.65	0.59
Val	276	A	T	.	-0.57	0.13	.	*	F	1.00	0.30
Thr	277	A	.	.	B	.	.	.	-0.34	0.56	.	*	.	-0.10	0.30
Phe	278	A	.	.	B	.	.	.	-1.16	0.63	.	*	.	-0.35	0.18
Phe	279	A	.	.	B	.	.	.	-0.77	1.31	.	*	.	-0.60	0.20
Gly	280	A	A	-1.58	0.67	.	*	.	-0.60	0.28
Ala	281	A	A	-1.53	0.87	.	*	.	-0.60	0.27
Leu	282	A	A	-1.61	0.77	*	.	.	-0.60	0.26
Lys	283	A	A	-1.30	0.41	*	.	.	-0.60	0.33
Leu	284	A	A	-0.99	0.41	.	.	.	-0.60	0.42
Leu	285	A	A	-1.03	0.34	*	.	.	-0.30	0.65

TABLE 10

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Met	1	A	0.73	-0.71	.	.	.	0.95	1.39
Asp	2	A	T	.	1.12	-0.66	*	.	.	1.15	1.56
Asp	3	A	T	.	1.62	-1.09	*	.	.	1.15	2.12
Ser	4	A	T	.	2.01	-1.51	.	.	.	1.15	4.19
Thr	5	A	T	.	2.40	-2.13	.	.	F	1.30	4.35
Glu	6	A	A	2.70	-1.73	*	*	F	0.90	4.51
Arg	7	A	A	2.81	-1.34	*	*	F	0.90	4.51
Glu	8	A	A	2.00	-1.73	*	*	F	0.90	6.12
Gln	9	A	A	1.99	-1.53	*	*	F	0.90	2.91
Ser	10	A	.	.	B	.	.	.	2.00	-1.04	*	*	F	0.90	2.15
Arg	11	A	.	.	B	.	.	.	1.33	-0.66	*	*	F	0.90	1.66
Leu	12	A	.	.	B	.	.	.	0.41	-0.09	*	*	F	0.45	0.51
Thr	13	A	.	.	B	.	.	.	0.46	0.20	*	*	F	-0.15	0.32
Ser	14	A	A	0.50	-0.19	*	*	.	0.30	0.32
Cys	15	A	A	0.91	-0.19	*	*	.	0.30	0.78
Leu	16	A	A	0.80	-0.87	*	*	F	0.90	1.06
Lys	17	A	A	1.61	-1.36	.	*	F	0.90	1.37
Lys	18	A	A	1.32	-1.74	.	*	F	0.90	4.44
Arg	19	A	A	1.67	-1.70	.	*	F	0.90	5.33
Glu	20	A	A	1.52	-2.39	.	*	F	0.90	5.33
Glu	21	A	A	2.38	-1.70	.	*	F	0.90	2.20
Met	22	A	A	2.33	-1.70	.	*	F	0.90	2.24
Lys	23	A	A	1.62	-1.70	*	*	F	0.90	2.24
Leu	24	A	A	0.66	-1.13	*	*	F	0.75	0.69
Lys	25	A	A	0.36	-0.49	.	*	F	0.45	0.52
Glu	26	A	A	.	B	.	.	.	-0.53	-0.71	*	*	.	0.60	0.35
Cys	27	A	A	.	B	.	.	.	-0.74	-0.03	*	*	.	0.30	0.30
Val	28	A	A	.	B	.	.	.	-1.00	-0.03	*	*	.	0.30	0.12
Ser	29	A	A	.	B	.	.	.	-0.08	0.40	*	*	.	-0.30	0.11
Ile	30	A	.	.	B	.	.	.	-0.08	0.40	*	*	.	-0.30	0.40
Leu	31	A	.	.	B	.	.	.	-0.08	-0.17	*	.	.	0.45	1.08
Pro	32	.	.	.	B	.	.	C	0.29	-0.81	*	.	F	1.10	1.39
Arg	33	T	.	.	0.93	-0.81	.	*	F	1.50	2.66
Lys	34	T	.	.	0.93	-1.07	.	*	F	1.84	4.98
Glu	35	C	0.97	-1.37	*	*	F	1.98	4.32
Ser	36	T	C	1.89	-1.16	*	*	F	2.52	1.64
Pro	37	T	C	1.80	-1.16	*	*	F	2.86	1.60

TABLE 10-continued

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Ser	38	T	T	.	1.39	-0.77	*	.	F	3.40	1.24
Val	39	A	T	.	1.39	-0.39	.	*	F	2.36	1.24
Arg	40	A	1.39	-0.77	*	*	F	2.46	1.60
Ser	41	A	1.34	-1.20	*	*	F	2.46	2.00
Ser	42	T	T	.	1.60	-1.16	.	*	F	3.06	2.67
Lys	43	T	T	.	1.09	-1.80	*	*	F	3.06	2.72
Asp	44	T	T	.	1.13	-1.11	*	*	F	3.40	1.67
Gly	45	A	T	.	0.43	-0.81	*	*	F	2.66	1.03
Lys	46	A	A	0.14	-0.70	.	.	F	1.77	0.52
Leu	47	A	A	0.13	-0.20	*	.	.	0.98	0.31
Leu	48	A	A	-0.72	0.29	*	.	.	0.04	0.46
Ala	49	A	A	-1.53	0.54	.	*	.	-0.60	0.19
Ala	50	A	A	-2.00	1.23	.	.	.	-0.60	0.19
Thr	51	A	A	-2.63	1.23	.	.	.	-0.60	0.19
Leu	52	A	A	-2.63	1.04	.	.	.	-0.60	0.19
Leu	53	A	A	-2.63	1.23	.	.	.	-0.60	0.15
Leu	54	A	A	-2.34	1.41	.	.	.	-0.60	0.09
Ala	55	A	A	-2.42	1.31	.	.	.	-0.60	0.14
Leu	56	A	A	-2.78	1.20	.	.	.	-0.60	0.09
Leu	57	A	T	.	-2.78	1.09	.	.	.	-0.20	0.06
Ser	58	A	T	.	-2.28	1.09	.	.	.	-0.20	0.05
Cys	59	A	T	.	-2.32	1.07	.	.	.	-0.20	0.09
Cys	60	A	T	.	-2.59	1.03	.	.	.	-0.20	0.08
Leu	61	.	.	B	B	.	.	.	-2.08	0.99	.	.	.	-0.60	0.04
Thr	62	.	.	B	B	.	.	.	-1.97	0.99	.	.	.	-0.60	0.11
Val	63	.	.	B	B	.	.	.	-1.91	1.20	.	.	.	-0.60	0.17
Val	64	.	.	B	B	.	.	.	-1.24	1.39	.	.	.	-0.60	0.33
Ser	65	.	.	B	B	.	.	.	-1.43	1.10	.	.	.	-0.60	0.40
Phe	66	A	.	.	B	.	.	.	-1.21	1.26	.	.	.	-0.60	0.40
Tyr	67	A	.	.	B	.	.	.	-1.49	1.11	.	.	.	-0.60	0.54
Gln	68	A	.	.	B	.	.	.	-1.44	0.97	.	.	.	-0.60	0.41
Val	69	A	.	.	B	.	.	.	-0.59	1.27	.	.	.	-0.60	0.39
Ala	70	A	.	.	B	.	.	.	-0.63	0.89	.	.	.	-0.60	0.43
Ala	71	A	.	.	B	.	.	.	0.07	0.56	.	*	.	-0.60	0.25
Leu	72	A	T	.	-0.50	0.16	.	.	.	0.10	0.55
Gln	73	A	T	.	-1.09	0.20	.	.	F	0.25	0.45
Gly	74	A	T	.	-0.53	0.20	.	.	F	0.25	0.45
Asp	75	A	T	.	-0.76	0.09	*	.	F	0.25	0.73
Leu	76	A	A	-0.06	0.09	*	.	F	-0.15	0.35
Ala	77	A	A	0.17	-0.31	*	.	.	0.30	0.69
Ser	78	A	A	0.17	-0.24	*	.	.	0.30	0.42
Leu	79	A	A	-0.30	-0.24	*	.	.	0.30	0.88
Arg	80	A	A	-0.30	-0.24	*	.	.	0.30	0.72
Ala	81	A	A	0.17	-0.34	*	.	.	0.30	0.93
Glu	82	A	A	0.72	-0.30	*	.	.	0.45	1.11
Leu	83	A	A	0.99	-0.49	*	.	.	0.30	0.77
Gln	84	A	A	1.21	0.01	*	.	.	-0.15	1.04
Gly	85	A	A	1.10	0.01	*	*	.	-0.30	0.61
His	86	A	A	1.73	0.01	*	*	.	-0.15	1.27
His	87	A	A	0.92	-0.67	*	.	.	0.75	1.47
Ala	88	A	A	1.52	-0.39	*	.	.	0.45	1.22
Glu	89	A	A	0.93	-0.39	*	.	.	0.45	1.39
Lys	90	A	A	0.93	-0.39	*	.	F	0.60	1.03
Leu	91	A	T	.	0.38	-0.46	*	.	.	0.85	1.01
Pro	92	A	T	.	0.07	-0.46	.	.	.	0.70	0.59
Ala	93	A	T	.	0.07	-0.03	.	.	.	0.70	0.29
Gly	94	A	T	.	-0.14	0.47	.	.	.	-0.20	0.36
Ala	95	A	-0.14	0.21	*	.	.	-0.10	0.36
Gly	96	A	0.08	-0.21	.	.	F	0.65	0.71
Ala	97	A	-0.06	-0.21	.	.	F	0.65	0.72
Pro	98	A	-0.28	-0.21	*	.	F	0.65	0.71
Lys	99	A	A	0.07	-0.03	.	.	F	0.45	0.59
Ala	100	A	A	0.66	-0.46	.	.	F	0.60	1.01
Gly	101	A	A	0.41	-0.96	.	.	F	0.90	1.13
Leu	102	A	A	0.79	-0.89	.	.	F	0.75	0.57
Glu	103	A	A	0.41	-0.46	*	.	F	0.45	0.88
Glu	104	A	A	-0.49	-0.46	*	.	F	0.45	0.89
Ala	105	A	A	-0.21	-0.24	.	.	.	0.30	0.81
Pro	106	A	A	-0.46	-0.44	.	.	.	0.30	0.67
Ala	107	A	A	0.01	0.06	.	.	.	-0.30	0.39
Val	108	A	A	-0.80	0.49	*	*	.	-0.60	0.38
Thr	109	A	A	-0.76	0.67	.	*	.	-0.60	0.20
Ala	110	A	A	-1.06	0.24	*	*	.	-0.30	0.40
Gly	111	A	A	-1.54	0.43	*	*	.	-0.60	0.38
Leu	112	A	A	-0.96	0.57	*	*	.	-0.60	0.23
Lys	113	.	A	B	-0.31	0.09	*	*	.	-0.30	0.39
Ile	114	.	A	B	-0.21	0.01	*	.	.	-0.30	0.61

TABLE 10-continued

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Phe	115	.	A	B	-0.21	0.01	*	.	.	0.15	1.15
Glu	116	.	A	C	-0.08	-0.17	*	.	F	1.25	0.58
Pro	117	.	A	C	0.39	0.26	*	*	F	1.10	1.28
Pro	118	C	0.34	0.00	*	.	F	2.20	1.47
Ala	119	T	C	0.89	-0.79	.	*	F	3.00	1.47
Pro	120	T	C	1.59	-0.36	.	*	F	2.25	0.94
Gly	121	T	T	.	1.29	-0.39	.	*	F	2.15	0.98
Glu	122	T	T	.	1.20	-0.43	.	.	F	2.00	1.30
Gly	123	C	1.41	-0.54	.	.	F	1.60	1.12
Asn	124	T	C	2.00	-0.57	.	.	F	1.50	1.97
Ser	125	T	C	1.91	-0.60	.	*	F	1.50	1.82
Ser	126	T	C	2.37	-0.21	.	*	F	1.54	2.47
Gln	127	T	C	2.37	-0.64	.	*	F	2.18	3.01
Asn	128	C	2.76	-0.64	.	.	F	2.32	3.61
Ser	129	T	C	2.87	-1.03	.	.	F	2.86	5.39
Arg	130	T	T	.	2.58	-1.41	*	.	F	3.40	6.09
Asn	131	T	T	.	2.02	-1.31	*	.	F	3.06	3.83
Lys	132	T	T	.	2.02	-1.07	*	.	F	2.72	2.12
Arg	133	T	.	.	1.68	-1.06	*	.	F	2.18	1.88
Ala	134	C	1.77	-0.63	*	.	F	1.64	1.15
Val	135	C	1.66	-0.60	*	.	F	1.15	0.89
Gln	136	C	1.66	-0.60	*	.	F	1.49	0.79
Gly	137	T	C	1.30	-0.60	*	.	F	2.18	1.35
Pro	138	T	C	0.84	-0.61	*	.	F	2.52	2.63
Glu	139	T	C	1.13	-0.83	*	.	F	2.86	1.50
Glu	140	T	T	.	1.74	-0.84	.	.	F	3.40	2.03
Thr	141	T	.	.	1.43	-0.51	.	.	F	2.86	2.06
Gly	142	T	T	.	1.08	-0.46	.	.	F	2.42	1.72
Ser	143	T	T	.	0.43	0.33	.	.	F	1.33	0.86
Tyr	144	T	T	.	0.22	0.97	.	.	.	0.54	0.44
Thr	145	T	T	.	-0.07	0.91	.	.	.	0.20	0.69
Phe	146	.	.	B	B	.	.	.	-0.57	1.40	.	.	.	-0.60	0.54
Val	147	.	.	B	B	.	.	.	-1.03	1.70	.	.	.	-0.60	0.29
Pro	148	.	.	B	B	.	.	.	-1.03	1.63	.	.	.	-0.60	0.16
Trp	149	A	.	.	B	.	.	.	-1.49	1.53	*	.	.	-0.60	0.25
Leu	150	A	.	.	B	.	.	.	-1.13	1.53	*	.	.	-0.60	0.29
Leu	151	A	.	.	B	.	.	.	-0.32	0.89	*	.	.	-0.30	0.38
Ser	152	A	0.19	0.46	*	.	.	0.20	0.71
Phe	153	T	.	.	0.10	-0.03	*	.	.	1.80	0.85
Lys	154	T	T	.	-0.20	-0.33	*	.	F	2.60	1.38
Arg	155	T	C	.	-0.20	-0.51	.	.	F	3.00	1.04
Gly	156	T	C	.	0.61	-0.21	.	.	F	2.25	0.99
Ser	157	A	.	.	.	T	.	.	0.91	-1.00	*	.	F	2.05	0.86
Ala	158	A	A	1.66	-1.00	*	.	F	1.35	0.76
Leu	159	A	A	1.61	-1.00	.	.	F	1.20	1.54
Glu	160	A	A	1.50	-1.43	.	.	F	0.90	1.98
Glu	161	A	A	1.89	-1.41	*	.	F	0.90	3.16
Lys	162	A	A	1.30	-1.91	*	.	F	0.90	7.66
Glu	163	A	A	1.08	-1.91	.	.	F	0.90	3.10
Asn	164	A	A	1.03	-1.23	*	*	F	0.90	1.48
Lys	165	A	A	1.08	-0.59	*	.	F	0.75	0.55
Ile	166	A	A	1.08	-0.59	*	*	.	0.60	0.63
Leu	167	A	A	0.72	-0.59	*	*	.	0.76	0.68
Val	168	A	A	0.38	-0.50	*	.	.	0.92	0.49
Lys	169	A	A	0.13	-0.07	*	*	F	0.93	0.69
Glu	170	A	T	.	-0.61	0.00	*	*	F	1.64	1.32
Thr	171	T	T	.	-0.42	0.10	.	*	F	1.60	1.54
Gly	172	T	T	.	-0.50	0.24	*	.	F	1.29	0.67
Tyr	173	T	T	.	0.11	0.93	*	*	.	0.68	0.27
Phe	174	.	.	B	B	.	.	.	-0.28	1.69	.	.	.	-0.28	0.29
Phe	175	.	.	B	B	.	.	.	-0.28	1.63	*	.	.	-0.44	0.29
Ile	176	.	.	B	B	.	.	.	-0.82	1.60	.	.	.	-0.60	0.32
Tyr	177	.	.	B	B	.	.	.	-1.29	1.49	.	.	.	-0.60	0.28
Gly	178	.	.	.	B	T	.	.	-1.29	1.39	.	.	.	-0.20	0.26
Gln	179	.	.	.	B	T	.	.	-0.90	1.36	.	.	.	-0.20	0.59
Val	180	.	.	.	B	.	.	C	-0.20	1.16	.	.	.	-0.40	0.54
Leu	181	.	.	.	B	.	.	C	0.73	0.40	.	.	.	-0.10	0.92
Tyr	182	T	T	.	0.67	-0.03	.	.	.	1.25	1.06
Thr	183	T	T	.	0.77	0.06	.	.	F	0.80	2.06
Asp	184	T	T	.	0.18	0.17	.	.	F	0.80	3.91
Lys	185	A	T	.	0.43	-0.01	.	.	F	1.00	2.52
Thr	186	A	A	0.90	-0.16	.	.	F	0.60	1.73
Tyr	187	A	A	1.11	-0.21	.	.	.	0.45	1.03
Ala	188	A	A	0.61	0.29	.	.	.	-0.30	0.70
Met	189	A	A	-0.28	0.97	.	.	.	-0.60	0.40
Gly	190	A	A	.	B	.	.	.	-0.32	1.17	*	.	.	-0.60	0.18
His	191	A	A	.	B	.	.	.	0.10	0.81	*	.	.	-0.60	0.31

TABLE 10-continued

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Leu	192	A	A	.	B	.	.	.	0.39	0.31	.	.	.	-0.30	0.61
Ile	193	A	A	.	B	.	.	.	1.02	-0.30	.	.	.	0.45	1.22
Gln	194	A	A	.	B	.	.	.	0.77	-0.73	.	.	.	0.75	1.80
Arg	195	A	A	.	B	.	.	.	1.08	-0.59	*	*	F	0.90	1.62
Lys	196	A	A	.	B	.	.	.	0.26	-0.77	*	*	F	0.90	3.14
Lys	197	A	A	.	B	.	.	.	0.37	-0.81	.	*	F	0.90	1.35
Val	198	.	A	B	B	.	.	.	0.91	-0.43	*	*	.	0.30	0.60
His	199	.	A	B	B	.	.	.	0.91	0.00	*	*	.	0.30	0.29
Val	200	.	A	B	B	.	.	.	0.80	0.00	*	*	.	0.30	0.25
Phe	201	.	.	B	B	.	.	.	-0.06	0.00	*	.	.	0.30	0.57
Gly	202	A	.	.	B	.	.	.	-0.40	0.04	.	.	.	-0.30	0.35
Asp	203	A	-0.36	-0.07	*	.	.	0.50	0.63
Glu	204	A	-1.18	-0.03	*	.	.	0.50	0.60
Leu	205	A	.	.	B	.	.	.	-0.63	-0.17	.	.	.	0.30	0.45
Ser	206	A	.	.	B	.	.	.	-0.74	-0.11	.	.	.	0.30	0.39
Leu	207	A	.	.	B	.	.	.	-1.10	0.57	.	*	.	-0.60	0.18
Val	208	A	.	.	B	.	.	.	-0.99	1.36	.	*	.	-0.60	0.19
Thr	209	A	.	.	B	.	.	.	-1.66	0.67	*	*	.	-0.60	0.28
Leu	210	A	.	.	B	.	.	.	-1.73	0.86	*	.	.	-0.60	0.18
Phe	211	A	.	.	B	.	.	.	-1.43	0.86	*	.	.	-0.60	0.17
Arg	212	A	.	.	B	.	.	.	-0.62	0.61	*	.	.	-0.60	0.21
Cys	213	.	.	.	B	T	.	.	-0.37	0.53	*	.	.	-0.20	0.41
Ile	214	.	.	.	B	T	.	.	-0.27	0.46	*	.	.	-0.20	0.46
Gln	215	.	.	.	B	T	.	.	0.54	0.10	*	.	.	0.10	0.37
Asn	216	.	.	.	B	.	C	.	0.93	0.10	*	.	.	0.05	1.19
Met	217	.	.	.	B	.	C	.	0.01	0.01	*	.	F	0.20	2.44
Pro	218	.	.	.	B	.	C	.	0.47	0.01	*	.	F	0.44	1.16
Glu	219	T	.	.	1.36	0.04	*	.	F	1.08	1.12
Thr	220	C	.	1.36	0.04	*	.	F	1.12	1.82
Leu	221	C	.	1.06	-0.17	*	.	F	1.96	1.89
Pro	222	T	.	.	0.99	-0.21	.	.	F	2.40	1.46
Asn	223	T	.	.	0.96	0.36	.	.	F	1.41	0.54
Asn	224	T	T	.	0.66	0.63	.	.	F	1.22	1.03
Ser	225	T	T	.	0.38	0.33	.	.	F	1.13	0.89
Cys	226	T	T	.	0.84	0.40	.	.	.	0.74	0.56
Tyr	227	T	T	.	0.17	0.43	.	.	.	0.20	0.35
Ser	228	A	-0.42	0.71	.	.	.	-0.40	0.18
Ala	229	A	A	-0.38	0.83	.	.	.	-0.60	0.34
Gly	230	A	A	-0.89	0.26	.	.	.	-0.30	0.43
Ile	231	A	A	-0.22	0.19	*	.	.	-0.30	0.27
Ala	232	A	A	0.02	-0.20	*	.	.	0.30	0.46
Lys	233	A	A	-0.02	-0.70	.	.	.	0.60	0.80
Leu	234	A	A	0.57	-0.70	.	.	F	0.90	1.13
Glu	235	A	A	0.91	-1.39	.	.	F	0.90	1.87
Glu	236	A	A	0.99	-1.89	.	.	F	0.90	1.62
Gly	237	A	A	1.58	-1.20	*	.	F	0.90	1.62
Asp	238	A	A	0.72	-1.49	*	.	F	0.90	1.62
Glu	239	A	A	0.94	-0.80	*	.	F	0.75	0.77
Leu	240	A	A	0.06	-0.30	*	.	.	0.30	0.79
Gln	241	A	A	-0.16	-0.04	*	.	.	0.30	0.33
Leu	242	A	A	0.30	0.39	*	.	.	-0.30	0.30
Ala	243	A	A	0.30	0.39	*	.	.	-0.30	0.70
Ile	244	A	A	0.30	-0.30	*	.	.	0.30	0.70
Pro	245	A	T	.	0.52	-0.30	.	*	F	1.00	1.37
Arg	246	A	T	.	0.52	-0.49	.	*	F	1.00	1.37
Glu	247	A	T	.	0.44	-0.59	*	*	F	1.30	3.38
Asn	248	A	T	.	0.73	-0.59	*	*	F	1.30	1.53
Ala	249	A	0.81	-0.63	*	*	.	0.95	1.05
Gln	250	A	1.02	0.06	*	*	.	-0.10	0.50
Ile	251	A	0.57	0.06	*	*	.	0.15	0.52
Ser	252	C	.	0.57	0.09	.	*	.	0.60	0.51
Leu	253	C	.	-0.29	-0.41	.	*	F	1.60	0.49
Asp	254	T	T	.	-0.01	-0.17	.	*	F	2.25	0.52
Gly	255	T	T	.	-0.71	-0.37	.	*	F	2.50	0.56
Asp	256	T	T	.	-0.52	0.03	.	*	F	1.65	0.59
Val	257	A	T	.	-0.57	0.13	.	*	F	1.00	0.30
Thr	258	A	.	.	B	.	.	.	-0.34	0.56	.	*	.	-0.10	0.30
Phe	259	A	.	.	B	.	.	.	-1.16	0.63	.	*	.	-0.35	0.18
Phe	260	A	.	.	B	.	.	.	-0.77	1.31	.	*	.	-0.60	0.20
Gly	261	A	A	-1.58	0.67	.	*	.	-0.60	0.28
Ala	262	A	A	-1.53	0.87	.	*	.	-0.60	0.27
Leu	263	A	A	-1.61	0.77	*	.	.	-0.60	0.26
Lys	264	A	A	-1.30	0.41	*	.	.	-0.60	0.33
Leu	265	A	A	-0.99	0.41	.	.	.	-0.60	0.42
Leu	266	A	A	-1.03	0.34	*	.	.	-0.30	0.65

In another embodiment, the invention provides antibodies that bind a polypeptide comprising, or alternatively, consisting of, an epitope-bearing portion of a polypeptide of the invention. The epitope of this polypeptide portion may be an immunogenic or antigenic epitope of a polypeptide of the invention. An "immunogenic epitope" is defined as a part of a protein that elicits an antibody response when the whole protein is the immunogen. On the other hand, a region of a protein molecule to which an antibody can bind is defined as an "antigenic epitope." The number of immunogenic epitopes of a protein generally is less than the number of antigenic epitopes. See, for instance, Geysen et al., *Proc. Natl. Acad. Sci. USA* 81:3998-4002 (1983).

As to the selection of polypeptides bearing an antigenic epitope (i.e., that contain a region of a protein molecule to which an antibody can bind), it is well known in that art that relatively short synthetic peptides that mimic part of a protein sequence are routinely capable of eliciting an antiserum that reacts with the partially mimicked protein. See, for instance, Sutcliffe, J. G., Shinnick, T. M., Green, N. and Learner, R. A. (1983) "Antibodies that react with predetermined sites on proteins", *Science*, 219:660-666. Peptides capable of eliciting protein-reactive sera are frequently represented in the primary sequence of a protein, can be characterized by a set of simple chemical rules, and are confined neither to immunodominant regions of intact proteins (i.e., immunogenic epitopes) nor to the amino or carboxyl terminals. Antigenic epitope-bearing peptides and polypeptides of the invention are therefore useful to raise antibodies, including monoclonal antibodies, that bind specifically to a polypeptide of the invention. See, for instance, Wilson et al., *Cell* 37:767-778 (1984) at 777.

In specific embodiments, antibodies of the present invention bind antigenic epitope-bearing peptides and polypeptides of B Lymphocyte Stimulator and preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids contained within the amino acid sequence of a B Lymphocyte Stimulator polypeptide. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof.

Non-limiting examples of antigenic polypeptides or peptides that can be used to generate B Lymphocyte Stimulator-specific antibodies and which may be bound by the antibodies of the invention include: a polypeptide comprising, or alternatively consisting of, amino acid residues from about Phe-115 to about Leu-147 in SEQ ID NO:3228; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ile-150 to about Tyr-163 in SEQ ID NO:3228; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Phe-194 in SEQ ID NO:3228; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Glu-223 to about Tyr-246 in SEQ ID NO:3228; and a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ser-271 to about Phe-278 in FIGS. 1A and 1B (SEQ ID NO:3228). In this context, "about" means the particularly recited ranges and ranges larger or smaller by several, a few, 5, 4, 3, 2 or 1 amino acid residues at either or both the amino- and carboxy-terminals. These polypeptide fragments have been determined to bear anti-

genic epitopes of the B Lymphocyte Stimulator polypeptide by the analysis of the Jameson-Wolf antigenic index, as disclosed Table 9, above.

Non-limiting examples of antigenic polypeptides or peptides that can be used to generate B Lymphocyte Stimulator-specific antibodies and which may be bound by the antibodies of the invention include: a polypeptide comprising, or alternatively consisting of, amino acid residues from about Pro-32 to about Leu-47 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Glu-116 to about Ser-143 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Phe-153 to about Tyr-173 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Pro-218 to about Tyr-227 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ala-232 to about Gln-241 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ile-244 to about Ala-249 in SEQ ID NO:3229; and a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ser-252 to about Val-257 in SEQ ID NO:3229. In this context, "about" means the particularly recited ranges and ranges larger or smaller by several, a few, 5, 4, 3, 2 or 1 amino acid residues at either or both the amino- and carboxy-terminals. These polypeptide fragments have been determined to bear antigenic epitopes of the B Lymphocyte Stimulator polypeptide by the analysis of the Jameson-Wolf antigenic index, as disclosed in Table 10 generated by the Protean component of the DNA*STAR computer program (as set forth above).

B Lymphocyte Stimulator epitope-bearing peptides and polypeptides may be produced by any conventional means. See, e.g., Houghten, R. A. (1985) General method for the rapid solid-phase synthesis of large numbers of peptides: specificity of antigen-antibody interaction at the level of individual amino acids. *Proc. Natl. Acad. Sci. USA* 82:5131-5135; this "Simultaneous Multiple Peptide Synthesis (SMPS)" process is further described in U.S. Pat. No. 4,631,211 to Houghten et al. (1986).

The present invention encompasses antibodies that bind polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid sequence of SEQ ID NO:3228, or an epitope of the polypeptide sequence encoded by a polynucleotide sequence contained in ATCC™ deposit No. 97768, or encoded by a polynucleotide that hybridizes to cDNA sequence contained in ATCC™ deposit No. 97768 (e.g., under hybridization conditions described herein).

The present invention also encompasses antibodies that bind polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid sequence of SEQ ID NO:3229, or an epitope of the polypeptide sequence encoded by a polynucleotide sequence contained in ATCC™ deposit No. 203518, or encoded by a polynucleotide that hybridizes to the cDNA sequence contained in ATCC™ deposit No. 203518 (e.g., under hybridization conditions described herein).

The term "epitopes," as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention encompasses antibodies that bind a polypeptide comprising an epitope. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies

described *infra*. (See, for example, Geysen et al., *Proc. Natl. Acad. Sci. USA* 81:3998-4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but does not necessarily exclude cross-reactivity with other antigens. Antigenic epitopes need not necessarily be immunogenic.

B Lymphocyte Stimulator polypeptide fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, *Proc. Natl. Acad. Sci. USA* 82:5131-5135 (1985), further described in U.S. Pat. No. 4,631,211).

In the present invention, antibodies of the present invention bind antigenic epitopes preferably containing a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes that may be bound by antibodies of the present invention are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., *Cell* 37:767-778 (1984); Sutcliffe et al., *Science* 219:660-666 (1983)).

Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., *supra*; Wilson et al., *supra*; Chow et al., *Proc. Natl. Acad. Sci. USA* 82:910-914; and Bittle et al., *J. Gen. Virol.* 66:2347-2354 (1985). Preferred immunogenic epitopes include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes of B Lymphocyte Stimulator may be presented for eliciting an antibody response together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

Epitope-bearing B Lymphocyte Stimulator polypeptides may be used to induce antibodies according to methods well known in the art including, but not limited to, *in vivo* immunization, *in vitro* immunization, and phage display methods. See, e.g., Sutcliffe et al., *supra*; Wilson et al., *supra*; and Bittle et al., *J. Gen. Virol.* 66:2347-2354 (1985). If *in vivo* immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemocyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl-N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent

such as glutaraldehyde. Animals such as rabbits, rats and mice are immunized with either free or carrier-coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 micrograms of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

As one of skill in the art will appreciate, and as discussed above, the antibodies of the present invention may bind polypeptides comprising an immunogenic or antigenic epitope fused to other polypeptide sequences. For example, the B Lymphocyte Stimulator polypeptides may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof), or albumin (including but not limited to recombinant human albumin or fragments or variants thereof (see, e.g., U.S. Pat. No. 5,876,969, issued Mar. 2, 1999, EP Patent 0 413 622, and U.S. Pat. No. 5,766,883, issued Jun. 16, 1998, herein incorporated by reference in their entirety)), resulting in chimeric polypeptides. Such fusion proteins may facilitate purification and may increase half-life *in vivo*. This has been shown for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Trautnecker et al., *Nature*, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG Fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion disulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulas et al., *J. Biochem.*, 270:3958-3964 (1995). Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin ("HA") tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., 1991, *Proc. Natl. Acad. Sci. USA* 88:8972-897). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix-binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto Ni²⁺ nitrilotriacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

In another embodiment, the antibodies of the present invention bind B Lymphocyte Stimulator polypeptides and/or the epitope-bearing fragments thereof that are fused with a heterologous antigen (e.g., polypeptide, carbohydrate, phospholipid, or nucleic acid). In specific embodiments, the heterologous antigen is an immunogen.

In a more specific embodiment, the heterologous antigen is the gp120 protein of HIV, or a fragment thereof.

In another embodiment, antibodies of the present invention bind B Lymphocyte Stimulator polypeptides and/or the epitope-bearing fragments thereof that are fused with polypeptide sequences of another TNF ligand family member (or biologically active fragments or variants thereof). In a specific embodiment, the antibodies of the present invention bind B Lymphocyte Stimulator polypeptides of the present invention are fused with a CD40L polypeptide sequence. In a preferred embodiment, the CD40L polypeptide sequence is soluble.

In another embodiment, antibodies of the present invention bind mutant B Lymphocyte Stimulator polypeptides that have been generated by random mutagenesis of a polynucleotide encoding the B Lymphocyte Stimulator polypeptide, by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, antibodies of the present invention bind one or more components, motifs, sections, parts, domains, fragments, etc., of B Lymphocyte Stimulator recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are, for example, TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPG, FasL, CD27L, CD30L, CD40L, 4-IBBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), AIM-II (International Publication No. WO 97/34911), APRIL (J. Exp. Med. 188(6):1185-1190), endokine-alpha (International Publication No. WO 98/07880), OPG, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-IBB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TR6 (International Publication No. WO 98/30694), TR7 (International Publication No. WO 98/41629), TRANK, TR9 (International Publication No. WO 98/56892), TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), TR12, CAD, and v-FLIP. In further embodiments, the heterologous molecules are any member of the TNF family.

In another preferred embodiment, antibodies of the present invention bind B Lymphocyte Stimulator polypeptides of the invention (including biologically active fragments or variants thereof), that are fused with soluble APRIL polypeptides (e.g., amino acid residues 105 through 250 of SEQ ID NO:3239), or biologically active fragments or variants thereof.

To improve or alter the characteristics of B Lymphocyte Stimulator polypeptides, protein engineering may be employed. Recombinant DNA technology known to those skilled in the art can be used to create novel mutant proteins or "mutins including single or multiple amino acid substitutions, deletions, additions or fusion proteins. Such modified polypeptides can show, e.g., enhanced activity or increased stability. In addition, they may be purified in higher yields and show better solubility than the corresponding natural polypeptide, at least under certain purification and storage conditions. For instance, for many proteins, including the extracellular domain or the mature form(s) of a secreted protein, it is known in the art that one or more amino acids may be deleted from the N-terminus or C-terminus without substantial loss of biological function. For instance, Ron et al., J.

Biol. Chem., 268:2984-2988 (1993) reported modified KGF proteins that had heparin binding activity even if 3, 8, or 27 amino-terminal amino acid residues were missing. Accordingly, antibodies of the present invention may bind B Lymphocyte Stimulator polypeptide mutants or variants generated by protein engineering.

In the present case, since the protein of the invention is a member of the TNF polypeptide family, deletions of N-terminal amino acids up to the Gly (G) residue at position 191 in SEQ ID NO:3228 may retain some biological activity such as, for example, the ability to stimulate lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, and cytotoxicity to appropriate target cells. Polypeptides having further N-terminal deletions including the Gly (G) residue would not be expected to retain biological activities because it is known that this residue in TNF-related polypeptides is in the beginning of the conserved domain required for biological activities. However, even if deletion of one or more amino acids from the N-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities may still be retained. Thus, the ability of the shortened protein to induce and/or bind to antibodies which recognize the complete or extracellular domain of the protein generally will be retained when less than the majority of the residues of the complete or extracellular domain of the protein are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete protein has such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of the B Lymphocyte Stimulator of SEQ ID NO:3228, up to the glycine residue at position 191 (Gly-191 residue from the amino terminus). In particular, the present invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues n¹-285 of SEQ ID NO:3228, where n¹ is an integer in the range of the amino acid position of amino acid residues 2-190 of the amino acid sequence in SEQ ID NO:3228. More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues 2-285, 3-285, 4-285, 5-285, 6-285, 7-285, 8-285, 9-285, 10-285, 11-285, 12-285, 13-285, 14-285, 15-285, 16-285, 17-285, 18-285, 19-285, 20-285, 21-285, 22-285, 23-285, 24-285, 25-285, 26-285, 27-285, 28-285, 29-285, 30-285, 31-285, 32-285, 33-285, 34-285, 35-285, 36-285, 37-285, 38-285, 39-285, 40-285, 41-285, 42-285, 43-285, 44-285, 45-285, 46-285, 47-285, 48-285, 49-285, 50-285, 51-285, 52-285, 53-285, 54-285, 55-285, 56-285, 57-285, 58-285, 59-285, 60-285, 61-285, 62-285, 63-285, 64-285, 65-285, 66-285, 67-285, 68-285, 69-285, 70-285, 71-285, 72-285, 73-285, 74-285, 75-285, 76-285, 77-285, 78-285, 79-285, 80-285, 81-285, 82-285, 83-285, 84-285, 85-285, 86-285, 87-285, 88-285, 89-285, 90-285, 91-285, 92-285, 93-285, 94-285, 95-285, 96-285, 97-285, 98-285, 99-285, 100-285, 101-285, 102-285, 103-285, 104-285, 105-285, 106-285, 107-285, 108-285, 109-285, 110-285, 111-285, 112-285, 113-285, 114-285, 115-285, 116-285, 117-285, 118-285, 119-285, 120-285, 121-285, 122-285, 123-285, 124-285, 125-285, 126-285, 127-285, 128-285, 129-285, 130-285, 131-285, 132-285, 133-285, 134-285, 135-285, 136-285, 137-285, 138-285, 139-285, 140-285, 141-285, 142-285, 143-285, 144-285, 145-285, 146-285, 147-285, 148-285, 149-285, 150-285, 151-285, 152-285, 153-285, 154-285, 155-285, 156-285,

157-285, 158-285, 159-285, 160-285, 161-285, 162-285, 163-285, 164-285, 165-285, 166-285, 167-285, 168-285, 169-285, 170-285, 171-285, 172-285, 173-285, 174-285, 175-285, 176-285, 177-285, 178-285, 179-285, 180-285, 181-285, 182-285, 183-285, 184-285, 185-285, 186-285, 187-285, 188-285, 189-285, and 190-285 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

Furthermore, since the predicted extracellular domain of the B Lymphocyte Stimulator polypeptides of the invention may itself elicit biological activity, deletions of N- and C-terminal amino acid residues from the predicted extracellular region of the polypeptide (spanning positions Gln-73 to Leu-285 of SEQ ID NO:3228) may retain some biological activity such as, for example, ligand binding, stimulation of lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, and modulation of cell replication or modulation of target cell activities. However, even if deletion of one or more amino acids from the N-terminus of the predicted extracellular domain of a B Lymphocyte Stimulator polypeptide results in modification or loss of one or more biological functions of the polypeptide, other functional activities may still be retained. Thus, the ability of the shortened polypeptides to induce and/or bind to antibodies which recognize the complete or mature or extracellular domains of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature or extracellular domains of the polypeptides are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of B Lymphocyte Stimulator shown in SEQ ID NO:3228, up to the glycine residue at position number 280. In particular, the present invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues n²-285 of SEQ ID NO:3228, where n² is an integer in the range of the amino acid position of amino acid residues 73-280 in SEQ ID NO:3228, and 73 is the position of the first residue from the N-terminus of the predicted extracellular domain of the B Lymphocyte Stimulator polypeptide (disclosed in SEQ ID NO:3228). More in particular, in certain embodiments, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues of Q-73 to L-285; G-74 to L-285; D-75 to L-285; L-76 to L-285; A-77 to L-285; S-78 to L-285; L-79 to L-285; R-80 to L-285; A-81 to L-285; E-82 to L-285; L-83 to L-285; Q-84 to L-285; G-85 to L-285; H-86 to L-285; H-87 to L-285; A-88 to L-285; E-89 to L-285; K-90 to L-285; L-91 to L-285; P-92 to L-285; A-93 to L-285; G-94 to L-285; A-95 to L-285; G-96 to L-285; A-97 to L-285; P-98 to L-285; K-99 to L-285; A-100 to L-285; G-101 to L-285; L-102 to L-285; E-103 to L-285; E-104 to L-285; A-105 to L-285; P-106 to L-285; A-107 to L-285; V-108 to L-285; T-109 to L-285; A-110 to L-285; G-111 to L-285; L-112 to L-285; K-113 to L-285; I-114 to L-285; F-115 to L-285; E-116 to L-285; P-117 to L-285; P-118 to L-285; A-119 to L-285; P-120 to L-285; G-121 to L-285; E-122 to L-285; G-123 to L-285; N-124 to L-285; S-125 to L-285; S-126 to L-285; Q-127 to L-285;

N-128 to L-285; S-129 to L-285; R-130 to L-285; N-131 to L-285; K-132 to L-285; R-133 to L-285; A-134 to L-285; V-135 to L-285; Q-136 to L-285; G-137 to L-285; P-138 to L-285; E-139 to L-285; E-140 to L-285; T-141 to L-285; V-142 to L-285; T-143 to L-285; Q-144 to L-285; D-145 to L-285; C-146 to L-285; L-147 to L-285; Q-148 to L-285; L-149 to L-285; I-150 to L-285; A-151 to L-285; D-152 to L-285; S-153 to L-285; E-154 to L-285; T-155 to L-285; P-156 to L-285; T-157 to L-285; I-158 to L-285; Q-159 to L-285; K-160 to L-285; G-161 to L-285; S-162 to L-285; Y-163 to L-285; T-164 to L-285; F-165 to L-285; V-166 to L-285; P-167 to L-285; W-168 to L-285; L-169 to L-285; L-170 to L-285; S-171 to L-285; F-172 to L-285; K-173 to L-285; R-174 to L-285; G-175 to L-285; S-176 to L-285; A-177 to L-285; L-178 to L-285; E-179 to L-285; E-180 to L-285; K-181 to L-285; E-182 to L-285; N-183 to L-285; K-184 to L-285; I-185 to L-285; L-186 to L-285; V-187 to L-285; K-188 to L-285; E-189 to L-285; T-190 to L-285; G-191 to L-285; Y-192 to L-285; F-193 to L-285; F-194 to L-285; I-195 to L-285; Y-196 to L-285; G-197 to L-285; Q-198 to L-285; V-199 to L-285; L-200 to L-285; Y-201 to L-285; T-202 to L-285; D-203 to L-285; K-204 to L-285; T-205 to L-285; Y-206 to L-285; A-207 to L-285; M-208 to L-285; G-209 to L-285; H-210 to L-285; L-211 to L-285; I-212 to L-285; Q-213 to L-285; R-214 to L-285; K-215 to L-285; K-216 to L-285; V-217 to L-285; H-218 to L-285; V-219 to L-285; F-220 to L-285; G-221 to L-285; D-222 to L-285; E-223 to L-285; L-224 to L-285; S-225 to L-285; L-226 to L-285; V-227 to L-285; T-228 to L-285; L-229 to L-285; F-230 to L-285; R-231 to L-285; C-232 to L-285; I-233 to L-285; Q-234 to L-285; N-235 to L-285; M-236 to L-285; P-237 to L-285; E-238 to L-285; T-239 to L-285; L-240 to L-285; P-241 to L-285; N-242 to L-285; N-243 to L-285; S-244 to L-285; C-245 to L-285; Y-246 to L-285; S-247 to L-285; A-248 to L-285; G-249 to L-285; I-250 to L-285; A-251 to L-285; K-252 to L-285; L-253 to L-285; E-254 to L-285; E-255 to L-285; G-256 to L-285; D-257 to L-285; E-258 to L-285; L-259 to L-285; Q-260 to L-285; L-261 to L-285; A-262 to L-285; I-263 to L-285; P-264 to L-285; R-265 to L-285; E-266 to L-285; N-267 to L-285; A-268 to L-285; Q-269 to L-285; I-270 to L-285; S-271 to L-285; L-272 to L-285; D-273 to L-285; G-274 to L-285; D-275 to L-285; V-276 to L-285; T-277 to L-285; F-278 to L-285; F-279 to L-285; and G-280 to L-285 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

Highly preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence least 80%, 85%, 90% identical and more preferably at least 95%, 96%, 97%, 98%, 99% or 100% identical to B Lymphocyte Stimulator polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228.

Preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 90% identical to a B Lymphocyte Stimulator polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228. More preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 95% identical to a B Lymphocyte Stimulator polypeptide having the amino acid sequence

at positions 134-285 of SEQ ID NO:3228. More preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 96% identical to a B Lymphocyte Stimulator polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228.

Additionally, more preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 97% to a B Lymphocyte Stimulator polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228. Additionally, more preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 98% to a B Lymphocyte Stimulator polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228. Additionally, more preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 99% identical to B Lymphocyte Stimulator polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228.

In specific embodiments, antibodies of the present invention bind polypeptides comprising, or alternatively consisting of, one of the following N-terminally deleted polypeptide fragments of B Lymphocyte Stimulator: amino acid residues Ala-71 through Leu-285, amino acid residues Ala-81 through Leu-285, amino acid residues Leu-112 through Leu-285, amino acid residues Ala-134 through Leu-285, amino acid residues Leu-147 through Leu-285, and amino acid residues Gly-161 through Leu-285 of SEQ ID NO:3228.

Similarly, many examples of biologically functional C-terminal deletion polypeptides are known. For instance, Interferon gamma shows up to ten times higher activities by deleting 8-10 amino acid residues from the carboxy terminus of the protein (Döbeli et al., *J. Biotechnology* 7:199-216 (1988)). Since the present protein is a member of the TNF polypeptide family, deletions of C-terminal amino acids up to the leucine residue at position 284 are expected to retain most if not all biological activity such as, for example, ligand binding, the ability to stimulate lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, and modulation of cell replication. Polypeptides having deletions of up to about 10 additional C-terminal residues (i.e., up to the glycine residue at position 274) also may retain some activity such as receptor binding, although such polypeptides would lack a portion of the conserved TNF domain which extends to about Leu-284 of SEQ ID NO:3228. However, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities may still be retained. Thus, the ability of the shortened protein to induce and/or bind to antibodies which recognize the complete or mature protein generally will be retained when less than the majority of the residues of the complete or mature protein are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete protein retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the B Lymphocyte Stimulator polypeptide of SEQ ID NO:3228, up to the glycine residue at position 274 (Gly-274). In particular, the present invention provides anti-

bodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues 1-m¹ of the amino acid sequence in SEQ ID NO:3228, where m¹ is any integer in the range of the amino acid position of amino acid residues 274-284 in SEQ ID NO:3228. More in particular, the invention provides antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues 1-274, 1-275, 1-276, 1-277, 1-278, 1-279, 1-280, 1-281, 1-282, 1-283 and 1-284 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

Also provided are antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively consisting of, B Lymphocyte Stimulator polypeptides with one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues n¹-m¹ of SEQ ID NO:3228, where n¹ and m¹ are integers as defined above. Also included are antibodies that bind a polypeptide comprising, or alternatively consisting of, a portion of the complete B Lymphocyte Stimulator amino acid sequence encoded by the deposited cDNA clone contained in ATCCTM Accession No. 97768 where this portion excludes from 1 to 190 amino acids from the amino terminus or from 1 to 11 amino acids from the C-terminus of the complete amino acid sequence (or any combination of these N-terminal and C-terminal deletions) encoded by the cDNA clone in the deposited plasmid.

Similarly, deletions of C-terminal amino acid residues of the predicted extracellular domain of B Lymphocyte Stimulator up to the leucine residue at position 79 of SEQ ID NO:3228 may retain some biological activity, such as, for example, ligand binding, stimulation of lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, and modulation of cell replication or modulation of target cell activities. Polypeptides having further C-terminal deletions including Leu-79 of SEQ ID NO:3228 would not be expected to retain biological activities.

However, even if deletion of one or more amino acids from the C-terminus of a polypeptide results in modification or loss of one or more biological functions of the polypeptide, other functional activities may still be retained. Thus, the ability of the shortened polypeptide to induce and/or bind to antibodies which recognize the complete, mature or extracellular forms of the polypeptide generally will be retained when less than the majority of the residues of the complete, mature or extracellular forms of the polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of the predicted extracellular domain retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the predicted extracellular domain of B Lymphocyte Stimulator polypeptide shown in SEQ ID NO:3228, up to the leucine residue at position 79 of SEQ ID NO:3228. In particular, the present invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues 73-m² of the amino acid sequence in SEQ ID NO:3228, where m² is any integer in the range of the amino acid position of amino acid residues 79 to 285 in the amino acid sequence in SEQ ID NO:3228, and

residue 78 is the position of the first residue at the C-terminus of the predicted extracellular domain of the B Lymphocyte Stimulator polypeptide (disclosed in SEQ ID NO:3228). More in particular, in certain embodiments, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues Q-73 to Leu-285; Q-73 to L-284; Q-73 to K-283; Q-73 to L-282; Q-73 to A-281; Q-73 to G-280; Q-73 to F-279; Q-73 to F-278; Q-73 to T-277; Q-73 to V-276; Q-73 to D-275; Q-73 to G-274; Q-73 to D-273; Q-73 to L-272; Q-73 to S-271; Q-73 to I-270; Q-73 to Q-269; Q-73 to A-268; Q-73 to N-267; Q-73 to E-266; Q-73 to R-265; Q-73 to P-264; Q-73 to I-263; Q-73 to A-262; Q-73 to L-261; Q-73 to Q-260; Q-73 to L-259; Q-73 to E-258; Q-73 to D-257; Q-73 to G-256; Q-73 to E-255; Q-73 to E-254; Q-73 to L-253; Q-73 to K-252; Q-73 to A-251; Q-73 to I-250; Q-73 to G-249; Q-73 to A-248; Q-73 to S-247; Q-73 to Y-246; Q-73 to C-245; Q-73 to S-244; Q-73 to N-243; Q-73 to N-242; Q-73 to P-241; Q-73 to L-240; Q-73 to T-239; Q-73 to E-238; Q-73 to P-237; Q-73 to M-236; Q-73 to N-235; Q-73 to Q-234; Q-73 to I-233; Q-73 to C-232; Q-73 to R-231; Q-73 to F-230; Q-73 to L-229; Q-73 to T-228; Q-73 to V-227; Q-73 to L-226; Q-73 to S-225; Q-73 to L-224; Q-73 to E-223; Q-73 to D-222; Q-73 to G-221; Q-73 to F-220; Q-73 to V-219; Q-73 to H-218; Q-73 to V-217; Q-73 to K-216; Q-73 to K-215; Q-73 to R-214; Q-73 to Q-213; Q-73 to I-212; Q-73 to L-211; Q-73 to H-210; Q-73 to G-209; Q-73 to M-208; Q-73 to A-207; Q-73 to Y-206; Q-73 to T-205; Q-73 to K-204; Q-73 to D-203; Q-73 to T-202; Q-73 to Y-201; Q-73 to L-200; Q-73 to V-199; Q-73 to Q-198; Q-73 to G-197; Q-73 to Y-196; Q-73 to I-195; Q-73 to F-194; Q-73 to F-193; Q-73 to Y-192; Q-73 to G-191; Q-73 to T-190; Q-73 to E-189; Q-73 to K-188; Q-73 to V-187; Q-73 to L-186; Q-73 to I-185; Q-73 to K-184; Q-73 to N-183; Q-73 to E-182; Q-73 to K-181; Q-73 to E-180; Q-73 to E-179; Q-73 to L-178; Q-73 to A-177; Q-73 to S-176; Q-73 to G-175; Q-73 to R-174; Q-73 to K-173; Q-73 to F-172; Q-73 to S-171; Q-73 to L-170; Q-73 to L-169; Q-73 to W-168; Q-73 to P-167; Q-73 to V-166; Q-73 to F-165; Q-73 to T-164; Q-73 to Y-163; Q-73 to S-162; Q-73 to G-161; Q-73 to K-160; Q-73 to Q-159; Q-73 to I-158; Q-73 to T-157; Q-73 to P-156; Q-73 to T-155; Q-73 to E-154; Q-73 to S-153; Q-73 to D-152; Q-73 to A-151; Q-73 to L-150; Q-73 to L-149; Q-73 to Q-148; Q-73 to L-147; Q-73 to C-146; Q-73 to D-145; Q-73 to Q-144; Q-73 to T-143; Q-73 to V-142; Q-73 to T-141; Q-73 to E-140; Q-73 to E-139; Q-73 to P-138; Q-73 to G-137; Q-73 to Q-136; Q-73 to V-135; Q-73 to A-134; Q-73 to R-133; Q-73 to K-132; Q-73 to N-131; Q-73 to R-130; Q-73 to S-129; Q-73 to N-128; Q-73 to Q-127; Q-73 to S-126; Q-73 to S-125; Q-73 to N-124; Q-73 to G-123; Q-73 to E-122; Q-73 to G-121; Q-73 to P-120; Q-73 to A-119; Q-73 to P-118; Q-73 to P-117; Q-73 to E-116; Q-73 to F-115; Q-73 to I-114; Q-73 to K-113; Q-73 to L-112; Q-73 to G-111; Q-73 to A-110; Q-73 to T-109; Q-73 to V-108; Q-73 to A-107; Q-73 to P-106; Q-73 to A-105; Q-73 to E-104; Q-73 to E-103; Q-73 to L-102; Q-73 to G-101; Q-73 to A-100; Q-73 to K-99; Q-73 to P-98; Q-73 to A-97; Q-73 to G-96; Q-73 to A-95; Q-73 to G-94; Q-73 to A-93; Q-73 to P-92; Q-73 to L-91; Q-73 to K-90; Q-73 to E-89; Q-73 to A-88; Q-73 to H-87; Q-73 to H-86; Q-73 to G-85; Q-73 to Q-84; Q-73 to L-83; Q-73 to E-82; Q-73 to A-81; Q-73 to R-80; and Q-73 to L-79 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

The invention also provides antibodies that bind polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of the predicted extracellular domain of B Lymphocyte Stimulator, which may be described generally as having residues n^2 - m^2 of SEQ ID NO:3228 where n^2 and m^2 are integers as defined above.

In another embodiment, antibodies of the present invention bind polypeptides consisting of a portion of the extracellular domain of the B Lymphocyte Stimulator amino acid sequence encoded by the cDNA plasmid contained in the deposit having ATCC™ accession no. 97768, where this portion excludes from 1 to about 206 amino acids from the amino terminus of the extracellular domain of the amino acid sequence encoded by the cDNA plasmid contained in the deposit having ATCC™ accession no. 97768, or from 1 to about 206 amino acids from the carboxy terminus of the extracellular domain of the amino acid sequence encoded by the cDNA plasmid contained in the deposit having ATCC™ accession no. 97768, or any combination of the above amino terminal and carboxy terminal deletions, of the entire extracellular domain of the amino acid sequence encoded by the cDNA plasmid contained in the deposit having ATCC™ accession no. 97768.

As mentioned above, even if deletion of one or more amino acids from the N-terminus of a polypeptide results in modification or loss of one or more functional activities (e.g., biological activity) of the polypeptide, other functions or biological activities may still be retained. Thus, the ability of a shortened B Lymphocyte Stimulator mutein to induce and/or bind to antibodies which recognize the full-length or mature forms or the extracellular domain of the polypeptide generally will be retained when less than the majority of the residues of the full-length or mature or extracellular domain of the polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a B Lymphocyte Stimulator mutein with a large number of deleted N-terminal amino acid residues may retain some functional (e.g., biological or immunogenic) activities. In fact, peptides composed of as few as six B Lymphocyte Stimulator amino acid residues may often evoke an immune response.

Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the predicted full-length amino acid sequence of the B Lymphocyte Stimulator shown in SEQ ID NO:3228, up to the glycine residue at position number 280 of the sequence shown SEQ ID NO:3228 and polynucleotides encoding such polypeptides. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues n^3 -285 of the sequence shown in SEQ ID NO:3228, where n^3 is an integer in the range of the amino acid position of amino acid residues 1 to 280 of the amino acid sequence in SEQ ID NO:3228.

More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues of D-2 to L-285; D-3 to L-285; S-4 to L-285; T-5 to L-285; E-6 to L-285; R-7 to L-285; E-8 to L-285; Q-9 to L-285; S-10 to L-285; R-11 to L-285; L-12 to L-285; T-13 to L-285; S-14 to L-285; C-15 to L-285; L-16 to L-285; K-17 to L-285; K-18 to L-285; R-19 to L-285; E-20 to L-285; E-21 to L-285; M-22 to L-285; K-23 to L-285; L-24 to L-285; K-25 to L-285; E-26 to L-285; C-27 to L-285; V-28 to L-285; S-29 to

L-285; I-30 to L-285; L-31 to L-285; P-32 to L-285; R-33 to L-285; K-34 to L-285; E-35 to L-285; S-36 to L-285; P-37 to L-285; S-38 to L-285; V-39 to L-285; R-40 to L-285; S-41 to L-285; S-42 to L-285; K-43 to L-285; D-44 to L-285; G-45 to L-285; K-46 to L-285; L-47 to L-285; L-48 to L-285; A-49 to L-285; A-50 to L-285; T-51 to L-285; L-52 to L-285; L-53 to L-285; L-54 to L-285; A-55 to L-285; L-56 to L-285; L-57 to L-285; S-58 to L-285; C-59 to L-285; C-60 to L-285; L-61 to L-285; T-62 to L-285; V-63 to L-285; V-64 to L-285; S-65 to L-285; F-66 to L-285; Y-67 to L-285; Q-68 to L-285; V-69 to L-285; A-70 to L-285; A-71 to L-285; L-72 to L-285; Q-73 to L-285; G-74 to L-285; D-75 to L-285; L-76 to L-285; A-77 to L-285; S-78 to L-285; L-79 to L-285; R-80 to L-285; A-81 to L-285; E-82 to L-285; L-83 to L-285; Q-84 to L-285; G-85 to L-285; H-86 to L-285; H-87 to L-285; A-88 to L-285; E-89 to L-285; K-90 to L-285; L-91 to L-285; P-92 to L-285; A-93 to L-285; G-94 to L-285; A-95 to L-285; G-96 to L-285; A-97 to L-285; P-98 to L-285; K-99 to L-285; A-100 to L-285; G-101 to L-285; L-102 to L-285; E-103 to L-285; E-104 to L-285; A-105 to L-285; P-106 to L-285; A-107 to L-285; V-108 to L-285; T-109 to L-285; A-110 to L-285; G-111 to L-285; L-112 to L-285; K-113 to L-285; I-114 to L-285; F-115 to L-285; E-116 to L-285; P-117 to L-285; P-118 to L-285; A-119 to L-285; P-120 to L-285; G-121 to L-285; E-122 to L-285; G-123 to L-285; N-124 to L-285; S-125 to L-285; S-126 to L-285; Q-127 to L-285; N-128 to L-285; S-129 to L-285; R-130 to L-285; N-131 to L-285; K-132 to L-285; R-133 to L-285; A-134 to L-285; V-135 to L-285; Q-136 to L-285; G-137 to L-285; P-138 to L-285; E-139 to L-285; E-140 to L-285; T-141 to L-285; V-142 to L-285; T-143 to L-285; Q-144 to L-285; D-145 to L-285; C-146 to L-285; L-147 to L-285; Q-148 to L-285; L-149 to L-285; I-150 to L-285; A-151 to L-285; D-152 to L-285; S-153 to L-285; E-154 to L-285; T-155 to L-285; P-156 to L-285; T-157 to L-285; I-158 to L-285; Q-159 to L-285; K-160 to L-285; G-161 to L-285; S-162 to L-285; Y-163 to L-285; T-164 to L-285; F-165 to L-285; V-166 to L-285; P-167 to L-285; W-168 to L-285; L-169 to L-285; L-170 to L-285; S-171 to L-285; F-172 to L-285; K-173 to L-285; R-174 to L-285; G-175 to L-285; S-176 to L-285; A-177 to L-285; L-178 to L-285; E-179 to L-285; E-180 to L-285; K-181 to L-285; E-182 to L-285; N-183 to L-285; K-184 to L-285; I-185 to L-285; L-186 to L-285; V-187 to L-285; K-188 to L-285; E-189 to L-285; T-190 to L-285; G-191 to L-285; Y-192 to L-285; F-193 to L-285; F-194 to L-285; I-195 to L-285; Y-196 to L-285; G-197 to L-285; Q-198 to L-285; V-199 to L-285; L-200 to L-285; Y-201 to L-285; T-202 to L-285; D-203 to L-285; K-204 to L-285; T-205 to L-285; Y-206 to L-285; A-207 to L-285; M-208 to L-285; G-209 to L-285; H-210 to L-285; L-211 to L-285; I-212 to L-285; Q-213 to L-285; R-214 to L-285; K-215 to L-285; K-216 to L-285; V-217 to L-285; H-218 to L-285; V-219 to L-285; F-220 to L-285; G-221 to L-285; L-222 to L-285; E-223 to L-285; L-224 to L-285; S-225 to L-285; L-226 to L-285; V-227 to L-285; T-228 to L-285; L-229 to L-285; F-230 to L-285; R-231 to L-285; C-232 to L-285; L-233 to L-285; Q-234 to L-285; N-235 to L-285; M-236 to L-285; P-237 to L-285; E-238 to L-285; T-239 to L-285; L-240 to L-285; P-241 to L-285; N-242 to L-285; N-243 to L-285; S-244 to L-285; C-245 to L-285; Y-246 to L-285; S-247 to L-285; A-248 to L-285; G-249 to L-285; I-250 to L-285; A-251 to L-285; K-252 to L-285; L-253 to L-285; E-254 to L-285; E-255 to L-285; G-256 to L-285; D-257 to L-285; E-258 to L-285; L-259 to L-285; Q-260 to L-285; L-261 to L-285; A-262 to L-285; I-263 to L-285; P-264 to L-285; R-265 to L-285; E-266 to L-285; N-267 to L-285; A-268 to L-285; Q-269 to L-285; I-270 to L-285; S-271 to L-285; L-272 to L-285;

D-273 to L-285; G-274 to L-285; D-275 to L-285; V-276 to L-285; T-277 to L-285; F-278 to L-285; F-279 to L-285; and G-280 to L-285 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more functional activities (e.g., biological activity) of the protein, other functional activities may still be retained. Thus, the ability of a shortened B Lymphocyte Stimulator mutein to induce and/or bind to antibodies which recognize the complete or mature form or the extracellular domain of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature form or the extracellular domain of the polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a B Lymphocyte Stimulator mutein with a large number of deleted C-terminal amino acid residues may retain some functional (e.g., biological or immunogenic) activities. In fact, peptides composed of as few as six B Lymphocyte Stimulator amino acid residues may often evoke an immune response.

Accordingly, the present invention further provides in another embodiment, antibodies that bind polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the B Lymphocyte Stimulator shown in SEQ ID NO:3228, up to the glutamic acid residue at position number 6, and polynucleotides encoding such polypeptides. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues 1-m³ of SEQ ID NO:3228, where m³ is an integer in the range of the amino acid position of amino acid residues 6-284 of the amino acid sequence in SEQ ID NO:3228.

More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues M-1 to L-284; M-1 to K-283; M-1 to L-282; M-1 to A-281; M-1 to G-280; M-1 to F-279; M-1 to F-278; M-1 to T-277; M-1 to V-276; M-1 to D-275; M-1 to G-274; M-1 to D-273; M-1 to L-272; M-1 to S-271; M-1 to I-270; M-1 to Q-269; M-1 to A-268; M-1 to N-267; M-1 to E-266; M-1 to R-265; M-1 to P-264; M-1 to I-263; M-1 to A-262; M-1 to L-261; M-1 to Q-260; M-1 to L-259; M-1 to E-258; M-1 to D-257; M-1 to G-256; M-1 to E-255; M-1 to E-254; M-1 to L-253; M-1 to K-252; M-1 to A-251; M-1 to I-250; M-1 to G-249; M-1 to A-248; M-1 to S-247; M-1 to Y-246; M-1 to C-245; M-1 to S-244; M-1 to N-243; M-1 to N-242; M-1 to P-241; M-1 to L-240; M-1 to T-239; M-1 to E-238; M-1 to P-237; M-1 to M-236; M-1 to N-235; M-1 to Q-234; M-1 to I-233; M-1 to C-232; M-1 to R-231; M-1 to F-230; M-1 to L-229; M-1 to T-228; M-1 to V-227; M-1 to L-226; M-1 to S-225; M-1 to L-224; M-1 to E-223; M-1 to D-222; M-1 to G-221; M-1 to F-220; M-1 to V-219; M-1 to H-218; M-1 to V-217; M-1 to K-216; M-1 to K-215; M-1 to R-214; M-1 to Q-213; M-1 to I-212; M-1 to L-211; M-1 to L-210; M-1 to G-209; M-1 to M-208; M-1 to A-207; M-1 to Y-206; M-1 to T-205; M-1 to K-204; M-1 to D-203; M-1 to T-202; M-1 to Y-201; M-1 to L-200; M-1 to V-199; M-1 to Q-198; M-1 to G-197; M-1 to Y-196; M-1 to I-195; M-1 to F-194; M-1 to

F-193; M-1 to Y-192; M-1 to G-191; M-1 to T-190; M-1 to E-189; M-1 to K-188; M-1 to V-187; M-1 to L-186; M-1 to I-185; M-1 to K-184; M-1 to N-183; M-1 to E-182; M-1 to K-181; M-1 to E-180; M-1 to E-179; M-1 to L-178; M-1 to A-177; M-1 to S-176; M-1 to G-175; M-1 to R-174; M-1 to K-173; M-1 to F-172; M-1 to S-171; M-1 to L-170; M-1 to L-169; M-1 to W-168; M-1 to P-167; M-1 to V-166; M-1 to F-165; M-1 to T-164; M-1 to Y-163; M-1 to S-162; M-1 to G-161; M-1 to K-160; M-1 to Q-159; M-1 to I-158; M-1 to T-157; M-1 to P-156; M-1 to T-155; M-1 to E-154; M-1 to S-153; M-1 to D-152; M-1 to A-151; M-1 to I-150; M-1 to L-149; M-1 to Q-148; M-1 to L-147; M-1 to C-146; M-1 to D-145; M-1 to Q-144; M-1 to T-143; M-1 to V-142; M-1 to T-141; M-1 to E-140; M-1 to E-139; M-1 to P-138; M-1 to G-137; M-1 to Q-136; M-1 to V-135; M-1 to A-134; M-1 to R-133; M-1 to K-132; M-1 to N-131; M-1 to R-130; M-1 to S-129; M-1 to N-128; M-1 to Q-127; M-1 to S-126; M-1 to S-125; M-1 to N-124; M-1 to G-123; M-1 to E-122; M-1 to G-121; M-1 to P-120; M-1 to A-119; M-1 to P-118; M-1 to P-117; M-1 to E-116; M-1 to F-115; M-1 to I-114; M-1 to K-113; M-1 to L-112; M-1 to G-111; M-1 to A-110; M-1 to T-109; M-1 to V-108; M-1 to A-107; M-1 to P-106; M-1 to A-105; M-1 to E-104; M-1 to E-103; M-1 to L-102; M-1 to G-101; M-1 to A-100; M-1 to K-99; M-1 to P-98; M-1 to A-97; M-1 to G-96; M-1 to A-95; M-1 to G-94; M-1 to A-93; M-1 to P-92; M-1 to L-91; M-1 to K-90; M-1 to E-89; M-1 to A-88; M-1 to H-87; M-1 to H-86; M-1 to G-85; M-1 to Q-84; M-1 to L-83; M-1 to E-82; M-1 to A-81; M-1 to R-80; M-1 to L-79; M-1 to S-78; M-1 to A-77; M-1 to L-76; M-1 to D-75; M-1 to G-74; M-1 to Q-73; M-1 to L-72; M-1 to A-71; M-1 to A-70; M-1 to V-69; M-1 to Q-68; M-1 to Y-67; M-1 to F-66; M-1 to S-65; M-1 to V-64; M-1 to V-63; M-1 to T-62; M-1 to L-61; M-1 to C-60; M-1 to C-59; M-1 to S-58; M-1 to L-57; M-1 to L-56; M-1 to A-55; M-1 to L-54; M-1 to L-53; M-1 to L-52; M-1 to T-51; M-1 to A-50; M-1 to A-49; M-1 to L-48; M-1 to L-47; M-1 to K-46; M-1 to G-45; M-1 to D-44; M-1 to K-43; M-1 to S-42; M-1 to S-41; M-1 to R-40; M-1 to V-39; M-1 to S-38; M-1 to P-37; M-1 to S-36; M-1 to E-35; M-1 to K-34; M-1 to R-33; M-1 to P-32; M-1 to L-31; M-1 to I-30; M-1 to S-29; M-1 to V-28; M-1 to C-27; M-1 to E-26; M-1 to K-25; M-1 to L-24; M-1 to K-23; M-1 to M-22; M-1 to E-21; M-1 to E-20; M-1 to R-19; M-1 to K-18; M-1 to K-17; M-1 to L-16; M-1 to C-15; M-1 to S-14; M-1 to T-13; M-1 to L-12; M-1 to R-11; M-1 to S-10; M-1 to Q-9; M-1 to E-8; M-1 to R-7; and M-1 to E-6 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

The invention also provides antibodies that bind polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of a B Lymphocyte Stimulator polypeptide, which may be described generally as having residues n^3 - m^3 of SEQ ID NO:3228, where n^3 and m^3 are integers as defined above.

Furthermore, since the predicted extracellular domain of the B Lymphocyte Stimulator polypeptide of SEQ ID NO:3229 may itself elicit functional activity (e.g., biological activity), deletions of N- and C-terminal amino acid residues from the predicted extracellular region of the polypeptide at positions Gln-73 to Leu-266 of SEQ ID NO:3229 may retain some functional activity, such as, for example, ligand binding, to stimulation of lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, modulation of cell replication, modulation of target cell activities and/or immunoge-

nicity. However, even if deletion of one or more amino acids from the N-terminus of the predicted extracellular domain of a B Lymphocyte Stimulator polypeptide results in modification or loss of one or more functional activities of the polypeptide, other functional activities may still be retained. Thus, the ability of the shortened polypeptides to induce and/or bind to antibodies which recognize the complete or mature or extracellular domains of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature or extracellular domains of the polypeptides are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of B Lymphocyte Stimulator shown in SEQ ID NO:3229, up to the glycine residue at position number 261. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues n^4 -266 of SEQ ID NO:3229, where n^4 is an integer in the range of the amino acid position of amino acid residues 73-261 of the amino acid sequence in SEQ ID NO:3229, and 261 is the position of the first residue from the N-terminus of the predicted extracellular domain B Lymphocyte Stimulator polypeptide (shown in SEQ ID NO:3229).

More in particular, in certain embodiments, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues of Q-73 to L-266; G-74 to L-266; D-75 to L-266; L-76 to L-266; A-77 to L-266; S-78 to L-266; L-79 to L-266; R-80 to L-266; A-81 to L-266; E-82 to L-266; L-83 to L-266; Q-84 to L-266; G-85 to L-266; H-86 to L-266; H-87 to L-266; A-88 to L-266; E-89 to L-266; K-90 to L-266; L-91 to L-266; P-92 to L-266; A-93 to L-266; G-94 to L-266; A-95 to L-266; G-96 to L-266; A-97 to L-266; P-98 to L-266; K-99 to L-266; A-100 to L-266; G-101 to L-266; L-102 to L-266; E-103 to L-266; E-104 to L-266; A-105 to L-266; P-106 to L-266; A-107 to L-266; V-108 to L-266; T-109 to L-266; A-110 to L-266; G-111 to L-266; L-112 to L-266; K-113 to L-266; I-114 to L-266; F-115 to L-266; E-116 to L-266; P-117 to L-266; P-118 to L-266; A-119 to L-266; P-120 to L-266; G-121 to L-266; E-122 to L-266; G-123 to L-266; N-124 to L-266; S-125 to L-266; S-126 to L-266; Q-127 to L-266; N-128 to L-266; S-129 to L-266; R-130 to L-266; N-131 to L-266; K-132 to L-266; R-133 to L-266; A-134 to L-266; V-135 to L-266; Q-136 to L-266; G-137 to L-266; P-138 to L-266; E-139 to L-266; E-140 to L-266; T-141 to L-266; G-142 to L-266; S-143 to L-266; Y-144 to L-266; T-145 to L-266; F-146 to L-266; V-147 to L-266; P-148 to L-266; W-149 to L-266; L-150 to L-266; L-151 to L-266; S-152 to L-266; F-153 to L-266; K-154 to L-266; R-155 to L-266; G-156 to L-266; S-157 to L-266; A-158 to L-266; L-159 to L-266; E-160 to L-266; E-161 to L-266; K-162 to L-266; E-163 to L-266; N-164 to L-266; K-165 to L-266; I-166 to L-266; L-167 to L-266; V-168 to L-266; K-169 to L-266; E-170 to L-266; T-171 to L-266; G-172 to L-266; Y-173 to L-266; F-174 to L-266; F-175 to L-266; I-176 to L-266; Y-177 to L-266; G-178 to L-266; Q-179 to L-266; V-180 to L-266; L-181 to L-266; Y-182 to L-266; T-183 to L-266; D-184 to L-266; K-185 to L-266; T-186 to L-266; Y-187 to L-266; A-188 to L-266; M-189 to L-266; G-190 to L-266; H-191 to L-266; L-192 to L-266; I-193 to L-266; Q-194 to L-266; R-195 to L-266; K-196 to L-266; K-197 to L-266; V-198 to L-266; H-199 to L-266;

V-200 to L-266; F-201 to L-266; G-202 to L-266; D-203 to L-266; E-204 to L-266; L-205 to L-266; S-206 to L-266; L-207 to L-266; V-208 to L-266; T-209 to L-266; L-210 to L-266; F-211 to L-266; R-212 to L-266; C-213 to L-266; I-214 to L-266; Q-215 to L-266; N-216 to L-266; M-217 to L-266; P-218 to L-266; E-219 to L-266; T-220 to L-266; L-221 to L-266; P-222 to L-266; N-223 to L-266; N-224 to L-266; S-225 to L-266; C-226 to L-266; Y-227 to L-266; S-228 to L-266; A-229 to L-266; G-230 to L-266; I-231 to L-266; A-232 to L-266; K-233 to L-266; L-234 to L-266; E-235 to L-266; E-236 to L-266; G-237 to L-266; D-238 to L-266; E-239 to L-266; L-240 to L-266; Q-241 to L-266; L-242 to L-266; A-243 to L-266; I-244 to L-266; P-245 to L-266; R-246 to L-266; E-247 to L-266; N-248 to L-266; A-249 to L-266; Q-250 to L-266; I-251 to L-266; S-252 to L-266; L-253 to L-266; D-254 to L-266; G-255 to L-266; D-256 to L-266; V-257 to L-266; T-258 to L-266; F-259 to L-266; F-260 to L-266; and G-261 to L-266 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

Similarly, deletions of C-terminal amino acid residues of the predicted extracellular domain of B Lymphocyte Stimulator up to the leucine residue at position 79 of SEQ ID NO:3229 may retain some functional activity, such as, for example, ligand binding, the ability to stimulate lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, modulation of cell replication, modulation of target cell activities and/or immunogenicity. Polypeptides having further C-terminal deletions including Leu-79 of SEQ ID NO:3229 would not be expected to retain biological activities.

However, even if deletion of one or more amino acids from the C-terminus of a polypeptide results in modification or loss of one or more functional activities (e.g., biological activity) of the polypeptide, other functional activities may still be retained. Thus, the ability of the shortened polypeptide to induce and/or bind to antibodies which recognize the complete, mature or extracellular forms of the polypeptide generally will be retained when less than the majority of the residues of the complete, mature or extracellular forms of the polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of the predicted extracellular domain retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues from the carboxy terminus of the amino acid sequence of the predicted extracellular domain of B Lymphocyte Stimulator shown in SEQ ID NO:3229, up to the leucine residue at position 79 of SEQ ID NO:3229. In particular, the present invention provides antibodies that bind polypeptides having the amino acid sequence of residues 73-m⁴ of the amino acid sequence in SEQ ID NO:3229, where m¹ is any integer in the range of the amino acid position of amino acid residues 79-265 of the amino acid sequence in SEQ ID NO:3229.

More in particular, in certain embodiments, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues Q-73 to L-265; Q-73 to K-264; Q-73 to L-263; Q-73 to A-262; Q-73 to G-261; Q-73 to F-260; Q-73 to F-259; Q-73 to T-258; Q-73 to V-257; Q-73 to D-256; Q-73 to G-255; Q-73 to D-254; Q-73 to L-253;

Q-73 to S-252; Q-73 to I-251; Q-73 to Q-250; Q-73 to A-249; Q-73 to N-248; Q-73 to E-247; Q-73 to R-246; Q-73 to P-245; Q-73 to I-244; Q-73 to A-243; Q-73 to L-242; Q-73 to Q-241; Q-73 to L-240; Q-73 to E-239; Q-73 to D-238; Q-73 to G-237; Q-73 to E-236; Q-73 to E-235; Q-73 to L-234; Q-73 to K-233; Q-73 to A-232; Q-73 to I-231; Q-73 to G-230; Q-73 to A-229; Q-73 to S-228; Q-73 to Y-227; Q-73 to C-226; Q-73 to S-225; Q-73 to N-224; Q-73 to N-223; Q-73 to P-222; Q-73 to L-221; Q-73 to T-220; Q-73 to E-219; Q-73 to P-218; Q-73 to M-217; Q-73 to N-216; Q-73 to Q-215; Q-73 to I-214; Q-73 to C-213; Q-73 to R-212; Q-73 to F-211; Q-73 to L-210; Q-73 to T-209; Q-73 to V-208; Q-73 to L-207; Q-73 to S-206; Q-73 to L-205; Q-73 to E-204; Q-73 to D-203; Q-73 to G-202; Q-73 to F-201; Q-73 to V-200; Q-73 to H-199; Q-73 to V-198; Q-73 to K-197; Q-73 to K-196; Q-73 to R-195; Q-73 to Q-194; Q-73 to I-193; Q-73 to L-192; Q-73 to H-191; Q-73 to G-190; Q-73 to Q-7389; Q-73 to A-188; Q-73 to Y-187; Q-73 to T-186; Q-73 to K-185; Q-73 to D-184; Q-73 to T-183; Q-73 to Y-182; Q-73 to L-181; Q-73 to V-180; Q-73 to Q-179; Q-73 to G-178; Q-73 to Y-177; Q-73 to I-176; Q-73 to F-175; Q-73 to F-174; Q-73 to Y-173; Q-73 to G-172; Q-73 to T-171; Q-73 to E-170; Q-73 to K-169; Q-73 to V-168; Q-73 to L-167; Q-73 to I-166; Q-73 to K-165; Q-73 to N-164; Q-73 to E-163; Q-73 to K-162; Q-73 to E-161; Q-73 to E-160; Q-73 to L-159; Q-73 to A-158; Q-73 to S-157; Q-73 to G-156; Q-73 to R-155; Q-73 to K-154; Q-73 to F-153; Q-73 to S-152; Q-73 to L-151; Q-73 to L-150; Q-73 to W-149; Q-73 to P-148; Q-73 to V-147; Q-73 to F-146; Q-73 to T-145; Q-73 to Y-144; Q-73 to S-143; Q-73 to G-142; Q-73 to T-141; Q-73 to E-140; Q-73 to E-139; Q-73 to P-138; Q-73 to G-137; Q-73 to Q-136; Q-73 to V-135; Q-73 to A-134; Q-73 to R-133; Q-73 to K-132; Q-73 to N-131; Q-73 to R-130; Q-73 to S-129; Q-73 to N-128; Q-73 to Q-127; Q-73 to S-126; Q-73 to S-125; Q-73 to N-124; Q-73 to G-123; Q-73 to E-122; Q-73 to G-121; Q-73 to P-120; Q-73 to A-119; Q-73 to P-118; Q-73 to P-117; Q-73 to E-116; Q-73 to F-115; Q-73 to I-114; Q-73 to K-113; Q-73 to L-112; Q-73 to G-111; Q-73 to A-110; Q-73 to T-109; Q-73 to V-108; Q-73 to A-107; Q-73 to P-106; Q-73 to A-105; Q-73 to E-104; Q-73 to E-103; Q-73 to L-102; Q-73 to G-101; Q-73 to A-100; Q-73 to K-99; Q-73 to P-98; Q-73 to A-97; Q-73 to G-96; Q-73 to A-95; Q-73 to G-94; Q-73 to A-93; Q-73 to P-92; Q-73 to L-91; Q-73 to K-90; Q-73 to E-89; Q-73 to A-88; Q-73 to H-87; Q-73 to H-86; Q-73 to G-85; Q-73 to Q-84; Q-73 to L-83; Q-73 to E-82; Q-73 to A-81; Q-73 to R-80; Q-73 to L-79; and Q-73 to S-78 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of the predicted extracellular domain of B Lymphocyte Stimulator, which may be described generally as having residues n⁴-m⁴ of SEQ ID NO:3229 where n⁴ and m⁴ are integers as defined above. 101341 In another embodiment, antibodies of the present invention bind polypeptides consisting of a portion of the extracellular domain of the B Lymphocyte Stimulator amino acid sequence encoded by the cDNA clone contained in the deposit having ATCCTM Accession No. 203518, where this portion excludes from 1 to about 260 amino acids from the amino terminus of the extracellular domain of the amino acid sequence encoded by cDNA clone contained in the deposit having ATCCTM Accession No. 203518, or from 1 to about 187 amino acids from the carboxy terminus of the extracellular domain of the amino acid

sequence encoded by cDNA clone contained in the deposit having ATCC™ Accession No. 203518, or any combination of the above amino terminal and carboxy terminal deletions, of the entire extracellular domain of the amino acid sequence encoded by the cDNA clone contained in the deposit having ATCC™ Accession No. 203518.

As mentioned above, even if deletion of one or more amino acids from the N-terminus of a polypeptide results in modification or loss of one or more functional activities (e.g., biological activity) of the polypeptide, other functional activities may still be retained. Thus, the ability of a shortened B Lymphocyte Stimulator polypeptide to induce and/or bind to antibodies which recognize the full-length or mature forms or the extracellular domain of the polypeptide generally will be retained when less than the majority of the residues of the full-length or mature or extracellular domain of the polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a B Lymphocyte Stimulator mutein with a large number of deleted N-terminal amino acid residues may retain functional (e.g., immunogenic) activities. In fact, peptides composed of as few as six B Lymphocyte Stimulator amino acid residues may often evoke an immune response.

Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the predicted full-length amino acid sequence of the B Lymphocyte Stimulator polypeptide shown in SEQ ID NO:3229, up to the glycine residue at position number 261 of the sequence shown SEQ ID NO:3229 and polynucleotides encoding such polypeptides. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues n⁵-266 of the sequence shown in SEQ ID NO:3229, where n⁵ is an integer in the range of the amino acid position of amino acid residues 1 to 261 of the amino acid sequence in SEQ ID NO:3229.

More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues of D-2 to L-266; D-3 to L-266; S-4 to L-266; T-5 to L-266; E-6 to L-266; R-7 to L-266; E-8 to L-266; Q-9 to L-266; S-10 to L-266; R-11 to L-266; L-12 to L-266; T-13 to L-266; S-14 to L-266; C-15 to L-266; L-16 to L-266; K-17 to L-266; K-18 to L-266; R-19 to L-266; E-20 to L-266; E-21 to L-266; M-22 to L-266; K-23 to L-266; L-24 to L-266; K-25 to L-266; E-26 to L-266; C-27 to L-266; V-28 to L-266; S-29 to L-266; I-30 to L-266; L-31 to L-266; P-32 to L-266; R-33 to L-266; K-34 to L-266; E-35 to L-266; S-36 to L-266; P-37 to L-266; S-38 to L-266; V-39 to L-266; R-40 to L-266; S-41 to L-266; S-42 to L-266; K-43 to L-266; D-44 to L-266; G-45 to L-266; K-46 to L-266; L-47 to L-266; L-48 to L-266; A-49 to L-266; A-50 to L-266; T-51 to L-266; L-52 to L-266; L-53 to L-266; L-54 to L-266; A-55 to L-266; L-56 to L-266; L-57 to L-266; S-58 to L-266; C-59 to L-266; C-60 to L-266; L-61 to L-266; T-62 to L-266; V-63 to L-266; V-64 to L-266; S-65 to L-266; F-66 to L-266; Y-67 to L-266; Q-68 to L-266; V-69 to L-266; A-70 to L-266; A-71 to L-266; L-72 to L-266; Q-73 to L-266; G-74 to L-266; D-75 to L-266; L-76 to L-266; A-77 to L-266; S-78 to L-266; L-79 to L-266; R-80 to L-266; A-81 to L-266; E-82 to L-266; L-83 to L-266; Q-84 to L-266; G-85 to L-266; H-86 to L-266; H-87 to L-266; A-88 to L-266; E-89 to L-266; K-90 to L-266; L-91 to L-266; P-92 to L-266; A-93 to L-266; G-94 to L-266; A-95 to L-266; G-96 to L-266; A-97 to L-266; P-98 to L-266; K-99 to L-266; A-100 to L-266; G-101

to L-266; L-102 to L-266; E-103 to L-266; E-104 to L-266; A-105 to L-266; P-106 to L-266; A-107 to L-266; V-108 to L-266; T-109 to L-266; A-110 to L-266; G-111 to L-266; L-112 to L-266; K-113 to L-266; I-114 to L-266; F-115 to L-266; E-116 to L-266; P-117 to L-266; P-118 to L-266; A-119 to L-266; P-120 to L-266; G-121 to L-266; E-122 to L-266; G-123 to L-266; N-124 to L-266; S-125 to L-266; S-126 to L-266; Q-127 to L-266; N-128 to L-266; S-129 to L-266; R-130 to L-266; N-131 to L-266; K-132 to L-266; R-133 to L-266; A-134 to L-266; V-135 to L-266; Q-136 to L-266; G-137 to L-266; P-138 to L-266; E-139 to L-266; E-140 to L-266; T-141 to L-266; G-142 to L-266; S-143 to L-266; Y-144 to L-266; T-145 to L-266; F-146 to L-266; V-147 to L-266; P-148 to L-266; W-149 to L-266; L-150 to L-266; L-151 to L-266; S-152 to L-266; F-153 to L-266; K-154 to L-266; R-155 to L-266; G-156 to L-266; S-157 to L-266; A-158 to L-266; L-159 to L-266; E-160 to L-266; E-161 to L-266; K-162 to L-266; E-163 to L-266; N-164 to L-266; K-165 to L-266; I-166 to L-266; L-167 to L-266; V-168 to L-266; K-169 to L-266; E-170 to L-266; T-171 to L-266; G-172 to L-266; Y-173 to L-266; F-174 to L-266; F-175 to L-266; I-176 to L-266; Y-177 to L-266; G-178 to L-266; Q-179 to L-266; V-180 to L-266; L-181 to L-266; Y-182 to L-266; T-183 to L-266; D-184 to L-266; K-185 to L-266; T-186 to L-266; Y-187 to L-266; A-188 to L-266; M-189 to L-266; G-190 to L-266; H-191 to L-266; L-192 to L-266; I-193 to L-266; Q-194 to L-266; R-195 to L-266; K-196 to L-266; K-197 to L-266; V-198 to L-266; H-199 to L-266; V-200 to L-266; F-201 to L-266; G-202 to L-266; D-203 to L-266; E-204 to L-266; L-205 to L-266; S-206 to L-266; L-207 to L-266; V-208 to L-266; T-209 to L-266; L-210 to L-266; F-211 to L-266; R-212 to L-266; C-213 to L-266; I-214 to L-266; Q-215 to L-266; N-216 to L-266; M-217 to L-266; P-218 to L-266; E-219 to L-266; T-220 to L-266; L-221 to L-266; P-222 to L-266; N-223 to L-266; N-224 to L-266; S-225 to L-266; C-226 to L-266; Y-227 to L-266; S-228 to L-266; A-229 to L-266; G-230 to L-266; I-231 to L-266; A-232 to L-266; K-233 to L-266; L-234 to L-266; E-235 to L-266; E-236 to L-266; G-237 to L-266; D-238 to L-266; E-239 to L-266; L-240 to L-266; Q-241 to L-266; L-242 to L-266; A-243 to L-266; I-244 to L-266; P-245 to L-266; R-246 to L-266; E-247 to L-266; N-248 to L-266; A-249 to L-266; Q-250 to L-266; I-251 to L-266; S-252 to L-266; L-253 to L-266; D-254 to L-266; G-255 to L-266; D-256 to L-266; V-257 to L-266; T-258 to L-266; F-259 to L-266; F-260 to L-266; and G-261 to L-266 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more functional activities (e.g., biological activities) of the protein, other functional activities may still be retained. Thus, the ability of a shortened B Lymphocyte Stimulator mutein to induce and/or bind to antibodies which recognize the complete or mature form or the extracellular domain of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature form or the extracellular domain of the polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a B Lymphocyte

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Stimulator mutein with a large number of deleted C-terminal amino acid residues may retain some functional (e.g., immunogenic) activities. In fact, peptides composed of as few as six B Lymphocyte Stimulator amino acid residues may often evoke an immune response.

Accordingly, the present invention further provides in another embodiment, antibodies that bind polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the B Lymphocyte Stimulator shown in SEQ ID NO:3229, up to the glutamic acid residue at position number 6, and polynucleotides encoding such polypeptides. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues 1-m⁵ of SEQ ID NO:3229, where m⁵ is an integer in the range of the amino acid position of amino acid residues 6 to 265 in the amino acid sequence of SEQ ID NO:3229.

More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues M-1 to L-265; M-1 to K-264; M-1 to L-263; M-1 to A-262; M-1 to G-261; M-1 to F-260; M-1 to F-259; M-1 to T-258; M-1 to V-257; M-1 to D-256; M-1 to G-255; M-1 to D-254; M-1 to L-253; M-1 to S-252; M-1 to I-251; M-1 to Q-250; M-1 to A-249; M-1 to N-248; M-1 to E-247; M-1 to R-246; M-1 to P-245; M-1 to I-244; M-1 to A-243; M-1 to L-242; M-1 to Q-241; M-1 to L-240; M-1 to E-239; M-1 to D-238; M-1 to G-237; M-1 to E-236; M-1 to E-235; M-1 to L-234; M-1 to K-233; M-1 to A-232; M-1 to I-231; M-1 to G-230; M-1 to A-229; M-1 to S-228; M-1 to Y-227; M-1 to C-226; M-1 to S-225; M-1 to N-224; M-1 to N-223; M-1 to P-222; M-1 to L-221; M-1 to T-220; M-1 to E-219; M-1 to P-218; M-1 to M-217; M-1 to N-216; M-1 to Q-215; M-1 to I-214; M-1 to C-213; M-1 to R-212; M-1 to F-211; M-1 to L-210; M-1 to T-209; M-1 to V-208; M-1 to L-207; M-1 to S-206; M-1 to L-205; M-1 to E-204; M-1 to D-203; M-1 to G-202; M-1 to F-201; M-1 to V-200; M-1 to H-199; M-1 to V-198; M-1 to K-197; M-1 to K-196; M-1 to R-195; M-1 to Q-194; M-1 to I-193; M-1 to L-192; M-1 to H-191; M-1 to G-190; M-1 to M-189; M-1 to A-188; M-1 to Y-187; M-1 to T-186; M-1 to K-185; M-1 to D-184; M-1 to T-183; M-1 to Y-182; M-1 to L-181; M-1 to V-180; M-1 to Q-179; M-1 to G-178; M-1 to Y-177; M-1 to I-176; M-1 to F-175; M-1 to F-174; M-1 to Y-173; M-1 to G-172; M-1 to T-171; M-1 to E-170; M-1 to K-169; M-1 to V-168; M-1 to L-167; M-1 to I-166; M-1 to K-165; M-1 to N-164; M-1 to E-163; M-1 to K-162; M-1 to E-161; M-1 to E-160; M-1 to L-159; M-1 to A-158; M-1 to S-157; M-1 to G-156; M-1 to R-155; M-1 to K-154; M-1 to F-153; M-1 to S-152; M-1 to L-151; M-1 to L-150; M-1 to W-149; M-1 to P-148; M-1 to V-147; M-1 to F-146; M-1 to T-145; M-1 to Y-144; M-1 to S-143; M-1 to G-142; M-1 to T-141; M-1 to E-140; M-1 to E-139; M-1 to P-138; M-1 to G-137; M-1 to Q-136; M-1 to V-135; M-1 to A-134; M-1 to R-133; M-1 to K-132; M-1 to N-131; M-1 to R-130; M-1 to S-129; M-1 to N-128; M-1 to Q-127; M-1 to S-126; M-1 to S-125; M-1 to N-124; M-1 to G-123; M-1 to E-122; M-1 to G-121; M-1 to P-120; M-1 to A-119; M-1 to P-118; M-1 to P-117; M-1 to E-116; M-1 to F-115; M-1 to I-114; M-1 to K-113; M-1 to L-112; M-1 to G-111; M-1 to A-110; M-1 to T-109; M-1 to V-108; M-1 to A-107; M-1 to P-106; M-1 to A-105; M-1 to E-104; M-1 to E-103; M-1 to L-102; M-1 to G-101; M-1 to A-100; M-1 to K-99; M-1 to P-98; M-1 to A-97; M-1 to G-96; M-1 to A-95; M-1 to G-94; M-1 to A-93; M-1 to P-92; M-1 to L-91; M-1 to K-90; M-1 to E-89; M-1 to A-88; M-1 to H-87; M-1 to H-86; M-1 to G-85; M-1 to Q-84; M-1 to L-83; M-1 to E-82; M-1 to A-81; M-1 to R-80; M-1 to L-79; M-1 to S-78; M-1 to A-77; M-1 to L-76;

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M-1 to D-75; M-1 to G-74; M-1 to Q-73; M-1 to L-72; M-1 to A-71; M-1 to A-70; M-1 to V-69; M-1 to Q-68; M-1 to Y-67; M-1 to F-66; M-1 to S-65; M-1 to V-64; M-1 to V-63; M-1 to T-62; M-1 to L-61; M-1 to C-60; M-1 to C-59; M-1 to S-58; M-1 to L-57; M-1 to L-56; M-1 to A-55; M-1 to L-54; M-1 to L-53; M-1 to L-52; M-1 to T-51; M-1 to A-50; M-1 to A-49; M-1 to L-48; M-1 to L-47; M-1 to K-46; M-1 to G-45; M-1 to D-44; M-1 to K-43; M-1 to S-42; M-1 to S-41; M-1 to R-40; M-1 to V-39; M-1 to S-38; M-1 to P-37; M-1 to S-36; M-1 to E-35; M-1 to K-34; M-1 to R-33; M-1 to P-32; M-1 to L-31; M-1 to I-30; M-1 to S-29; M-1 to V-28; M-1 to C-27; M-1 to E-26; M-1 to K-25; M-1 to L-24; M-1 to K-23; M-1 to M-22; M-1 to E-21; M-1 to E-20; M-1 to R-19; M-1 to K-18; M-1 to K-17; M-1 to L-16; M-1 to C-15; M-1 to S-14; M-1 to T-13; M-1 to L-12; M-1 to R-11; M-1 to S-10; M-1 to Q-9; M-1 to E-8; M-1 to R-7; and M-1 to E-6 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

The invention also provides antibodies that bind polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of a B Lymphocyte Stimulator polypeptide, which may be described generally as having residues n⁵-m⁵ of SEQ ID NO:3229, where n⁵ and m⁵ are integers as defined above.

In additional embodiments, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues 134-m⁶ of SEQ ID NO:3228, where m⁶ is an integer from 140 to 285, corresponding to the position of the amino acid residue in SEQ ID NO:3228. For example, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues A-134 to Leu-285; A-134 to L-284; A-134 to K-283; A-134 to L-282; A-134 to A-281; A-134 to G-280; A-134 to F-279; A-134 to F-278; A-134 to T-277; A-134 to V-276; A-134 to D-275; A-134 to G-274; A-134 to D-273; A-134 to L-272; A-134 to S-271; A-134 to I-270; A-134 to Q-269; A-134 to A-268; A-134 to N-267; A-134 to E-266; A-134 to R-265; A-134 to P-264; A-134 to I-263; A-134 to A-262; A-134 to L-261; A-134 to Q-260; A-134 to L-259; A-134 to E-258; A-134 to D-257; A-134 to G-256; A-134 to E-255; A-134 to E-254; A-134 to L-253; A-134 to K-252; A-134 to A-251; A-134 to I-250; A-134 to G-249; A-134 to A-248; A-134 to S-247; A-134 to Y-246; A-134 to C-245; A-134 to S-244; A-134 to N-243; A-134 to N-242; A-134 to P-241; A-134 to L-240; A-134 to T-239; A-134 to E-238; A-134 to P-237; A-134 to M-236; A-134 to N-235; A-134 to Q-234; A-134 to I-233; A-134 to C-232; A-134 to R-231; A-134 to F-230; A-134 to L-229; A-134 to T-228; A-134 to V-227; A-134 to L-226; A-134 to S-225; A-134 to L-224; A-134 to E-223; A-134 to D-222; A-134 to G-221; A-134 to F-220; A-134 to V-219; A-134 to H-218; A-134 to V-217; A-134 to K-216; A-134 to K-215; A-134 to R-214; A-134 to Q-213; A-134 to I-212; A-134 to L-211; A-134 to H-210; A-134 to G-209; A-134 to M-208; A-134 to A-207; A-134 to Y-206; A-134 to T-205; A-134 to K-204; A-134 to D-203; A-134 to T-202; A-134 to Y-201; A-134 to L-200; A-134 to V-199; A-134 to Q-198; A-134 to G-197; A-134 to Y-196; A-134 to I-195; A-134 to F-194; A-134 to F-193; A-134 to Y-192; A-134 to G-191; A-134 to T-190; A-134 to E-189; A-134 to K-188; A-134 to V-187; A-134 to L-186; A-134 to I-185; A-134 to K-184; A-134 to N-183; A-134 to E-182; A-134 to K-181; A-134 to E-180; A-134 to E-179; A-134 to L-178; A-134 to A-177; A-134 to

S-176; A-134 to G-175; A-134 to R-174; A-134 to K-173; A-134 to F-172; A-134 to S-171; A-134 to L-170; A-134 to L-169; A-134 to W-168; A-134 to P-167; A-134 to V-166; A-134 to F-165; A-134 to T-164; A-134 to Y-163; A-134 to S-162; A-134 to G-161; A-134 to K-160; A-134 to Q-159; A-134 to I-158; A-134 to T-157; A-134 to P-156; A-134 to T-155; A-134 to E-154; A-134 to S-153; A-134 to D-152; A-134 to A-151; A-134 to I-150; A-134 to L-149; A-134 to Q-148; A-134 to L-147; A-134 to C-146; A-134 to D-145; A-134 to Q-144; A-134 to T-143; A-134 to V-142; A-134 to T-141; and A-134 to E-140 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

In additional embodiments, antibodies of the present invention may bind polypeptide fragments comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues: M-1 to C-15; D-2 to L-16; D-3 to K-17; S-4 to K-18; T-5 to R-19; E-6 to E-20; R-7 to E-21; E-8 to M-22; Q-9 to K-23; S-10 to L-24; R-11 to K-25; L-12 to E-26; T-13 to C-27; S-14 to V-28; C-15 to S-29; L-16 to I-30; K-17 to L-31; K-18 to P-32; R-19 to R-33; E-20 to K-34; E-21 to E-35; M-22 to S-36; K-23 to P-37; L-24 to S-38; K-25 to V-39; E-26 to R-40; C-27 to S-41; V-28 to S-42; S-29 to K-43; I-30 to D-44; L-31 to G-45; P-32 to K-46; R-33 to L-47; K-34 to L-48; E-35 to A-49; S-36 to A-50; P-37 to T-51; S-38 to L-52; V-39 to L-53; R-40 to L-54; S-41 to A-55; S-42 to L-56; K-43 to L-57; D-44 to S-58; G-45 to C-59; K-46 to C-60; L-47 to L-61; L-48 to T-62; A-49 to V-63; A-50 to V-64; T-51 to S-65; L-52 to F-66; L-53 to Y-67; L-54 to Q-68; A-55 to V-69; L-56 to A-70; L-57 to A-71; S-58 to L-72; C-59 to Q-73; C-60 to G-74; L-61 to D-75; T-62 to L-76; V-63 to A-77; V-64 to S-78; S-65 to L-79; F-66 to R-80; Y-67 to A-81; Q-68 to E-82; V-69 to L-83; A-70 to Q-84; A-71 to G-85; L-72 to H-86; Q-73 to H-87; G-74 to A-88; D-75 to E-89; L-76 to K-90; A-77 to L-91; S-78 to P-92; L-79 to A-93; R-80 to G-94; A-81 to A-95; E-82 to G-96; L-83 to A-97; Q-84 to P-98; G-85 to K-99; H-86 to A-100; H-87 to G-101; A-88 to L-102; E-89 to E-103; K-90 to E-104; L-91 to A-105; P-92 to P-106; A-93 to A-107; G-94 to V-108; A-95 to T-109; G-96 to A-110; A-97 to G-111; P-98 to L-112; K-99 to K-113; A-100 to I-114; G-101 to F-115; L-102 to E-116; E-103 to P-117; E-104 to P-118; A-105 to A-119; P-106 to P-120; A-107 to G-121; V-108 to E-122; T-109 to G-123; A-110 to N-124; G-111 to S-125; L-112 to S-126; K-113 to Q-127; I-114 to N-128; F-115 to S-129; E-116 to R-130; P-117 to N-131; P-118 to K-132; A-119 to R-133; P-120 to A-134; G-121 to V-135; E-122 to Q-136; G-123 to G-137; N-124 to P-138; S-125 to E-139; S-126 to E-140; Q-127 to T-141; N-128 to V-142; S-129 to T-143; R-130 to Q-144; N-131 to D-145; K-132 to C-146; R-133 to L-147; A-134 to Q-148; V-135 to L-149; Q-136 to I-150; G-137 to A-151; P-138 to D-152; E-139 to S-153; E-140 to E-154; T-141 to T-155; V-142 to P-156; T-143 to T-157; Q-144 to L-158; D-145 to Q-159; C-146 to K-160; L-147 to G-161; Q-148 to S-162; L-149 to Y-163; I-150 to T-164; A-151 to F-165; D-152 to V-166; S-153 to P-167; E-154 to W-168; T-155 to L-169; P-156 to L-170; T-157 to S-171; I-158 to F-172; Q-159 to K-173; K-160 to R-174; G-161 to G-175; S-162 to S-176; Y-163 to A-177; T-164 to L-178; F-165 to E-179; V-166 to E-180; P-167 to K-181; W-168 to E-182; L-169 to N-183; L-170 to K-184; S-171 to I-185; F-172 to L-186; K-173 to V-187; R-174 to K-188; G-175 to E-189; S-176 to T-190; A-177 to G-191; L-178 to Y-192; E-179 to F-193; E-180 to F-194;

K-181 to I-195; E-182 to Y-196; N-183 to G-197; K-184 to Q-198; I-185 to V-199; L-186 to L-200; V-187 to Y-201; K-188 to T-202; E-189 to D-203; T-190 to K-204; G-191 to T-205; Y-192 to Y-206; F-193 to A-207; F-194 to M-208; I-195 to G-209; Y-196 to H-210; G-197 to L-211; Q-198 to I-212; V-199 to Q-213; L-200 to R-214; Y-201 to K-215; T-202 to K-216; D-203 to V-217; K-204 to H-218; T-205 to V-219; Y-206 to F-220; A-207 to G-221; M-208 to D-222; G-209 to E-223; H-210 to L-224; L-211 to S-225; I-212 to L-226; Q-213 to V-227; R-214 to T-228; K-215 to L-229; K-216 to F-230; V-217 to R-231; H-218 to C-232; V-219 to I-233; F-220 to Q-234; G-221 to N-235; D-222 to M-236; E-223 to P-237; L-224 to E-238; S-225 to T-239; L-226 to L-240; V-227 to P-241; T-228 to N-242; L-229 to N-243; F-230 to S-244; R-231 to C-245; C-232 to Y-246; I-233 to S-247; Q-234 to A-248; N-235 to G-249; M-236 to I-250; P-237 to A-251; E-238 to K-252; T-239 to L-253; L-240 to E-254; P-241 to E-255; N-242 to G-256; N-243 to D-257; S-244 to E-258; C-245 to L-259; Y-246 to Q-260; S-247 to L-261; A-248 to A-262; G-249 to I-263; I-250 to P-264; A-251 to R-265; K-252 to E-266; L-253 to N-267; E-254 to A-268; E-255 to Q-269; G-256 to I-270; D-257 to S-271; E-258 to L-272; L-259 to D-273; Q-260 to G-274; L-261 to D-275; A-262 to V-276; I-263 to T-277; P-264 to F-278; R-265 to F-279; E-266 to G-280; N-267 to A-281; A-268 to L-282; Q-269 to K-283; I-270 to L-284; and S-271 to L-285 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

In additional embodiments, antibodies of the present invention may bind polypeptide fragments comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues: M-1 to C-15; D-2 to L-16; D-3 to K-17; S-4 to K-18; T-5 to R-19; E-6 to E-20; R-7 to E-21; E-8 to M-22; Q-9 to K-23; S-10 to L-24; R-11 to K-25; L-12 to E-26; T-13 to C-27; S-14 to V-28; C-15 to S-29; L-16 to I-30; K-17 to L-31; K-18 to P-32; R-19 to R-33; E-20 to K-34; E-21 to E-35; M-22 to S-36; K-23 to P-37; L-24 to S-38; K-25 to V-39; E-26 to R-40; C-27 to S-41; V-28 to S-42; S-29 to K-43; I-30 to D-44; L-31 to G-45; P-32 to K-46; R-33 to L-47; K-34 to L-48; E-35 to A-49; S-36 to A-50; P-37 to T-51; S-38 to L-52; V-39 to L-53; R-40 to L-54; S-41 to A-55; S-42 to L-56; K-43 to L-57; D-44 to S-58; G-45 to C-59; K-46 to C-60; L-47 to L-61; L-48 to T-62; A-49 to V-63; A-50 to V-64; T-51 to S-65; L-52 to F-66; L-53 to Y-67; L-54 to Q-68; A-55 to V-69; L-56 to A-70; L-57 to A-71; S-58 to L-72; C-59 to Q-73; C-60 to G-74; L-61 to D-75; T-62 to L-76; V-63 to A-77; V-64 to S-78; S-65 to L-79; F-66 to R-80; Y-67 to A-81; Q-68 to E-82; V-69 to L-83; A-70 to Q-84; A-71 to G-85; L-72 to H-86; Q-73 to H-87; G-74 to A-88; D-75 to E-89; L-76 to K-90; A-77 to L-91; S-78 to P-92; L-79 to A-93; R-80 to G-94; A-81 to A-95; E-82 to G-96; L-83 to A-97; Q-84 to P-98; G-85 to K-99; H-86 to A-100; H-87 to G-101; A-88 to L-102; E-89 to E-103; K-90 to E-104; L-91 to A-105; P-92 to P-106; A-93 to A-107; G-94 to V-108; A-95 to T-109; G-96 to A-110; A-97 to G-111; P-98 to L-112; K-99 to K-113; A-100 to I-114; G-101 to F-115; L-102 to E-116; E-103 to P-117; E-104 to P-118; A-105 to A-119; P-106 to P-120; A-107 to G-121; V-108 to E-122; T-109 to G-123; A-110 to N-124; G-111 to S-125; L-112 to S-126; K-113 to Q-127; I-114 to N-128; F-115 to S-129; E-116 to R-130; P-117 to N-131; P-118 to K-132; A-119 to R-133; P-120 to A-134; G-121 to V-135; E-122 to Q-136; G-123 to G-137; N-124 to P-138;

S-125 to E-139; S-126 to E-140; Q-127 to T-141; N-128 to G-142; S-129 to S-143; R-130 to Y-144; N-131 to T-145; K-132 to F-146; R-133 to V-147; A-134 to P-148; V-135 to W-149; Q-136 to L-150; G-137 to L-151; P-138 to S-152; E-139 to F-153; E-140 to K-154; T-141 to R-155; G-142 to G-156; S-143 to S-157; Y-144 to A-158; T-145 to L-159; F-146 to E-160; V-147 to E-161; P-148 to K-162; W-149 to E-163; L-150 to N-164; L-151 to K-165; S-152 to I-166; F-153 to L-167; K-154 to V-168; R-155 to K-169; G-156 to E-170; S-157 to T-171; A-158 to G-172; L-159 to Y-173; E-160 to F-174; E-161 to F-175; K-162 to I-176; E-163 to Y-177; N-164 to G-178; K-165 to Q-179; I-166 to V-180; L-167 to L-181; V-168 to Y-182; K-169 to T-183; E-170 to D-184; T-171 to K-185; G-172 to T-186; Y-173 to Y-187; F-174 to A-188; F-175 to M-189; I-176 to G-190; Y-177 to H-191; G-178 to L-192; Q-179 to I-193; V-180 to Q-194; L-181 to R-195; Y-182 to K-196; T-183 to K-197; D-184 to V-198; K-185 to H-199; T-186 to V-200; Y-187 to F-201; A-188 to G-202; M-189 to D-203; G-190 to E-204; H-191 to L-205; L-192 to S-206; I-193 to L-207; Q-194 to V-208; R-195 to T-209; K-196 to L-210; K-197 to F-211; V-198 to R-212; H-199 to C-213; V-200 to I-214; F-201 to Q-215; G-202 to N-216; D-203 to M-217; E-204 to P-218; L-205 to E-219; S-206 to T-220; L-207 to L-221; V-208 to P-222; T-209 to N-223; L-210 to N-224; F-211 to S-225; R-212 to C-226; C-213 to Y-227; I-214 to S-228; Q-215 to A-229; N-216 to G-230; M-217 to I-231; P-218 to A-232; E-219 to K-233; T-220 to L-234; L-221 to E-235; P-222 to E-236; N-223 to G-237; N-224 to D-238; S-225 to E-239; C-226 to L-240; Y-227 to Q-241; S-228 to L-242; A-229 to A-243; G-230 to I-244; I-231 to P-245; A-232 to R-246; K-233 to E-247; L-234 to N-248; E-235 to A-249; E-236 to Q-250; G-237 to I-251; D-238 to S-252; E-239 to L-253; L-240 to D-254; Q-241 to G-255; L-242 to D-256; A-243 to V-257; I-244 to T-258; P-245 to F-259; R-246 to F-260; E-247 to G-261; N-248 to A-262; A-249 to L-263; Q-250 to K-264; I-251 to L-265; and S-252 to L-266 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

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L-101; R-88 to T-102; G-89 to A-103; S-90 to G-104; A-91 to V-105; T-92 to K-106; P-93 to L-107; A-94 to L-108; A-95 to T-109; A-96 to P-110; G-97 to A-111; A-98 to A-112; P-99 to P-113; E-100 to R-114; L-101 to P-115; T-102 to H-116; A-103 to N-117; G-104 to S-118; V-105 to S-119; K-106 to R-120; L-107 to G-121; L-108 to H-122; T-109 to R-123; P-110 to N-124; A-111 to R-125; A-112 to R-126; P-113 to A-127; R-114 to F-128; P-115 to Q-129; H-116 to G-130; N-117 to P-131; S-118 to E-132; S-119 to E-133; R-120 to T-134; G-121 to E-135; H-122 to Q-136; R-123 to D-137; N-124 to V-138; R-125 to D-139; R-126 to L-140; A-127 to S-141; F-128 to A-142; Q-129 to P-143; G-130 to P-144; P-131 to A-145; E-132 to P-146; E-133 to C-147; T-134 to L-148; E-135 to P-149; Q-136 to G-150; D-137 to C-151; V-138 to R-152; D-139 to H-153; L-140 to S-154; S-141 to Q-155; A-142 to H-156; P-143 to D-157; P-144 to D-158; A-145 to N-159; P-146 to G-160; C-147 to M-161; L-148 to N-162; P-149 to L-163; G-150 to R-164; C-151 to N-165; R-152 to I-166; H-153 to I-167; S-154 to Q-168; Q-155 to D-169; H-156 to C-170; D-157 to L-171; D-158 to Q-172; N-159 to L-173; G-160 to I-174; M-161 to A-175; N-162 to D-176; L-163 to S-177; R-164 to D-178; N-165 to T-179; I-166 to P-180; I-167 to A-181; Q-168 to L-182; D-169 to E-183; C-170 to E-184; L-171 to K-185; Q-172 to E-186; L-173 to N-187; I-174 to K-188; A-175 to I-189; D-176 to V-190; S-177 to V-191; D-178 to R-192; T-179 to Q-193; P-180 to T-194; A-181 to G-195; L-182 to Y-196; E-183 to F-197; E-184 to F-198; K-185 to I-199; E-186 to Y-200; N-187 to S-201; K-188 to Q-202; I-189 to V-203; V-190 to L-204; V-191 to Y-205; R-192 to T-206; Q-193 to D-207; T-194 to P-208; G-195 to I-209; Y-196 to F-210; F-197 to A-211; F-198 to M-212; I-199 to G-213; Y-200 to H-214; S-201 to V-215; Q-202 to I-216; V-203 to Q-217; L-204 to R-218; Y-205 to K-219; T-206 to K-220; D-207 to V-221; P-208 to H-222; I-209 to V-223; F-210 to F-224; A-211 to G-225; M-212 to D-226; G-213 to E-227; H-214 to L-228; V-215 to S-229; I-216 to L-230; Q-217 to V-231; R-218 to T-232; K-219 to L-233; K-220 to F-234; V-221 to R-235; H-222 to C-236; V-223 to I-237; F-224 to Q-238; G-225 to N-239; D-226 to M-240; E-227 to P-241; L-228 to K-242; S-229 to T-243; L-230 to L-244; V-231 to P-245; T-232 to N-246; L-233 to N-247; F-234 to S-248; R-235 to C-249; C-236 to Y-250; I-237 to S-251; Q-238 to A-252; N-239 to G-253; M-240 to I-254; P-241 to A-255; K-242 to R-256; T-243 to L-257; L-244 to E-258; P-245 to E-259; N-246 to G-260; N-247 to D-261; S-248 to E-262; C-249 to I-263; Y-250 to Q-264; S-251 to L-265; A-252 to A-266; G-253 to I-267; I-254 to P-268; A-255 to R-269; R-256 to E-270; L-257 to N-271; E-258 to A-272; E-259 to Q-273; G-260 to I-274; D-261 to S-275; E-262 to R-276; I-263 to N-277; Q-264 to G-278; L-265 to D-279; A-266 to D-280; I-267 to T-281; P-268 to F-282; R-269 to F-283; E-270 to G-284; N-271 to A-285; A-272 to L-286; Q-273 to K-287; I-274 to L-288; and S-275 to L-289 of SEQ ID NO:38. The present invention is also directed to antibodies that bind B Lymphocyte Stimulator polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of B Lymphocyte Stimulator polypeptides described above.

It will be recognized by one of ordinary skill in the art that some amino acid sequences of the B Lymphocyte Stimulator polypeptides can be varied without significant effect of the structure or function of the polypeptide. If such differences in sequence are contemplated, it should be remembered that there will be critical areas on the polypeptide which determine activity.

Thus, the invention further includes antibodies that bind variations of B Lymphocyte Stimulator polypeptides which show B Lymphocyte Stimulator polypeptide functional activity (e.g., biological activity) or which include regions of B Lymphocyte Stimulator polypeptide such as the polypeptide fragments described herein. Such mutants include deletions, insertions, inversions, repeats, and type substitutions selected according to general rules known in the art so as have little effect on activity. For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie, J. U. et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," *Science* 247:1306-1310 (1990), wherein the authors indicate that there are two main approaches for studying the tolerance of an amino acid sequence to change. The first method relies on the process of evolution, in which mutations are either accepted or rejected by natural selection. The second approach uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene and selections or screens to identify sequences that maintain functionality.

As the authors state, these studies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at a certain position of the protein. For example, most buried amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Other such phenotypically silent substitutions are described in Bowie, J. U. et al., supra, and the references cited therein. Typically seen as conservative substitutions are the replacements, one for another, among the aliphatic amino acids Ala, Val, Leu and Ile; interchange of the hydroxyl residues Ser and Thr, exchange of the acidic residues Asp and Glu, substitution between the amide residues Asn and Gln, exchange of the basic residues Lys and Arg and replacements among the aromatic residues Phe, Tyr.

Thus, antibodies of the present invention may bind fragments, derivatives or analogs of the polypeptide of SEQ ID NO:3228, or that encoded by the deposited cDNA plasmid, such as (i) polypeptides in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) polypeptides in which one or more of the amino acid residues includes a substituent group, or (iii) polypeptides in which the extracellular domain of the polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol), or (iv) polypeptides in which the additional amino acids are fused to the extracellular domain of the polypeptide, such as an IgG Fc fusion region peptide or leader or secretory sequence or a sequence which is employed for purification of the extracellular domain of the polypeptide or a proprotein sequence.

Antibodies of the present invention may bind fragments, derivatives or analogs of the polypeptide of SEQ ID NO:3229, or that encoded by the deposited cDNA plasmid, such as (i) polypeptides in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) polypeptides in which one or more of the amino acid residues includes a substituent group, or (iii) polypeptides in which the extracellular domain of the polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol), or (iv) polypeptides in which the additional amino acids are fused to

the extracellular domain of the polypeptide, such as, a soluble biologically active fragment of another TNF ligand family member (e.g., CD40 Ligand), an IgG Fc fusion region peptide or leader or secretory sequence or a sequence which is employed for purification of the extracellular domain of the polypeptide or a proprotein sequence. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein.

Thus, the antibodies of the invention may bind B Lymphocyte Stimulator polypeptides that include one or more amino acid substitutions, deletions or additions, either from natural mutations or human manipulation. As indicated, changes are preferably of a minor nature, such as conservative amino acid substitutions that do not significantly affect the folding or activity of the protein (see Table 13).

TABLE 13

Conservative Amino Acid Substitutions.	
Aromatic	Phenylalanine
	Tryptophan
Hydrophobic	Tyrosine
	Leucine
	Isoleucine
	Valine
Polar	Glutamine
	Asparagine
Basic	Arginine
	Lysine
	Histidine
Acidic	Aspartic Acid
	Glutamic Acid
Small	Alanine
	Serine
	Threonine
	Methionine
	Glycine

In one embodiment of the invention, antibodies of the present invention bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of a B Lymphocyte Stimulator polypeptide having an amino acid sequence which contains at least one conservative amino acid substitution, but not more than 50 conservative amino acid substitutions, even more preferably, not more than 40 conservative amino acid substitutions, still more preferably, not more than 30 conservative amino acid substitutions, and still even more preferably, not more than 20 conservative amino acid substitutions. In one embodiment of the invention, antibodies of the present invention bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of a B Lymphocyte Stimulator polypeptide having an amino acid sequence which contains at least one conservative amino acid substitution, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 conservative amino acid substitutions.

For example, site directed changes at the amino acid level of B Lymphocyte Stimulator can be made by replacing a particular amino acid with a conservative substitution. Antibodies of the present invention may bind B Lymphocyte Stimulator amino acid sequences containing conservative substitution mutations of the polypeptide of SEQ ID NO:3228 including: M1 replaced with A, G, I, L, S, T, or V; D2 replaced with E; D3 replaced with E; S4 replaced with A, G, I, L, T, M, or V; T5 replaced with A, G, I, L, S, M, or V; E6 replaced with D; R7 replaced with H, or K; E8 replaced with D; Q9 replaced with N; S10 replaced with A, G, I, L, T, M, or V; R11 replaced with H, or K; L12 replaced with A, G, I, S, T, M, or V; T13 replaced with A, G, I, L, S, M, or V; S14 replaced with A, G, I, L, T, M, or V; I.16 replaced with A, G, S, T, M,

or V; K17 replaced with H, or R; K18 replaced with H, or R; R19 replaced with H, or K; E20 replaced with D; E21 replaced with D; M22 replaced with A, G, I, L, S, T, or V; K23 replaced with H, or R; L24 replaced with A, G, I, S, T, M, or V; K25 replaced with H, or R; E26 replaced with D; V28 replaced with A, G, I, L, S, T, or M; S29 replaced with A, G, I, L, T, M, or V; L30 replaced with A, G, L, S, T, M, or V; L31 replaced with A, G, I, S, T, M, or V; R33 replaced with H, or K; K34 replaced with H, or R; E35 replaced with D; S36 replaced with A, G, I, L, T, M, or V; S38 replaced with A, G, I, L, T, M, or V; V39 replaced with A, G, I, L, S, T, or M; R40 replaced with H, or K; S41 replaced with A, G, I, L, T, M, or V; S42 replaced with A, G, I, L, T, M, or V; K43 replaced with H, or R; D44 replaced with E; G45 replaced with A, L, S, T, M, or V; K46 replaced with H, or R; L47 replaced with A, G, I, S, T, M, or V; L48 replaced with A, G, I, S, T, M, or V; A49 replaced with G, I, L, S, T, M, or V; A50 replaced with G, I, L, S, T, M, or V; T51 replaced with A, G, I, L, S, M, or V; L52 replaced with A, G, I, L, S, T, M, or V; L53 replaced with A, G, I, S, T, M, or V; L54 replaced with A, G, I, S, T, M, or V; A55 replaced with G, I, L, S, T, M, or V; L56 replaced with A, G, I, S, T, M, or V; L57 replaced with A, G, I, S, T, M, or V; S58 replaced with A, G, I, L, T, M, or V; L61 replaced with A, G, I, S, T, M, or V; T62 replaced with A, G, I, L, S, M, or V; V63 replaced with A, G, I, L, S, T, or M; V64 replaced with A, G, I, L, S, T, or M; S65 replaced with A, G, I, L, T, M, or V; F66 replaced with W, or Y; Y67 replaced with F, or W; Q68 replaced with N; V69 replaced with A, G, I, L, S, T, or M; A70 replaced with G, I, L, S, T, M, or V; A71 replaced with G, I, L, S, T, M, or V; L72 replaced with A, G, I, S, T, M, or V; Q73 replaced with N; G74 replaced with A, I, L, S, T, M, or V; D75 replaced with E; L76 replaced with A, G, I, S, T, M, or V; A77 replaced with G, I, L, S, T, M, or V; S78 replaced with A, G, I, L, T, M, or V; L79 replaced with A, G, I, S, T, M, or V; R80 replaced with H, or K; A81 replaced with G, I, L, S, T, M, or V; E82 replaced with D; L83 replaced with A, G, I, S, T, M, or V; Q84 replaced with N; G85 replaced with A, I, L, S, T, M, or V; H86 replaced with K, or R; H87 replaced with K, or R; A88 replaced with G, I, L, S, T, M, or V; E89 replaced with D; K90 replaced with H, or R; L91 replaced with A, G, I, S, T, M, or V; A93 replaced with G, I, L, S, T, M, or V; G94 replaced with A, I, L, S, T, M, or V; A95 replaced with G, I, L, S, T, M, or V; G 96 replaced with A, I, L, S, T, M, or V; A97 replaced with G, I, L, S, T, M, or V; K99 replaced with H, or R; A100 replaced with G, I, L, S, T, M, or V; G101 replaced with A, I, L, S, T, M, or V; L102 replaced with A, G, I, S, T, M, or V; E103 replaced with D; E104 replaced with D; A105 replaced with G, I, L, S, T, M, or V; A107 replaced with G, I, L, S, T, M, or V; V108 replaced with A, G, I, L, S, T, or M; T109 replaced with A, G, I, L, S, M, or V; A110 replaced with G, I, L, S, T, M, or V; G111 replaced with A, I, L, S, T, M, or V; L112 replaced with A, G, I, S, T, M, or V; K113 replaced with H or R; I114 replaced with A, G, L, S, T, M, or V; F115 replaced with W, or Y; E116 replaced with D; A119 replaced with G, I, L, S, T, M, or V; G121 replaced with A, I, S, T, M, or V; E122 replaced with D; G123 replaced with A, I, L, S, T, M, or V; N124 replaced with Q; S125 replaced with A, G, I, L, T, M, or V; S126 replaced with A, G, I, L, T, M, or V; Q127 replaced with N; N128 replaced with Q; S129 replaced with A, G, I, L, T, M, or V; R130 replaced with H, or K; N131 replaced with Q; K132 replaced with H or R; R133 replaced with H, or K; A134 replaced with G, I, L, S, T, M, or V; V135 replaced with A, G, I, L, S, T, or M; Q136 replaced with N; G137 replaced with A, I, L, S, T, M, or V; E139 replaced with D; E140 replaced with D; T141 replaced with A, G, I, L, S, M, or V; V142 replaced with A, G, I, L, S, T, or M; T143 replaced with A, G, I, L, S, M, or V; Q144 replaced with N; D145 replaced

with E; L147 replaced with A, G, I, S, T, M, or V; Q148 replaced with N; L149 replaced with A, G, I, S, T, M, or V; I150 replaced with A, G, L, S, T, M, or V; A151 replaced with G, I, L, S, T, M, or V; D152 replaced with E; S153 replaced with A, G, I, L, T, M, or V; E154 replaced with D; T155 replaced with A, G, I, L, S, M, or V; T157 replaced with A, G, I, S, M, or V; I158 replaced with A, G, L, S, T, M, or V; Q159 replaced with N; K160 replaced with H, or R; G161 replaced with A, I, L, S, T, M, or V; S162 replaced with A, G, I, L, T, M, or V; Y163 replaced with F, or W; T164 replaced with A, G, I, L, S, M, or V; F165 replaced with W, or Y; V166 replaced with A, G, I, L, S, T, or M; W168 replaced with F, or Y; L169 replaced with A, G, I, S, T, M, or V; L170 replaced with A, G, I, L, S, T, M, or V; S171 replaced with A, G, I, L, T, M, or V; F172 replaced with W, or Y; K173 replaced with H, or R; R174 replaced with H, or K; G175 replaced with A, I, L, S, T, M, or V; S176 replaced with A, G, I, L, T, M, or V; A177 replaced with G, I, L, S, T, M, or V; L178 replaced with A, G, I, S, T, M, or V; E179 replaced with D; E180 replaced with D; K181 replaced with H, or R; E182 replaced with D; N183 replaced with Q; K184 replaced with H, or R; I185 replaced with A, G, L, S, T, M, or V; L186 replaced with A, G, I, S, T, M, or V; V187 replaced with A, G, I, L, S, T, or M; K188 replaced with H, or R; E189 replaced with D; T190 replaced with A, G, I, L, S, M, or V; G191 replaced with A, I, L, S, T, M, or V; Y192 replaced with F, or W; F193 replaced with W, or Y; F194 replaced with W, or Y; I195 replaced with A, G, L, S, T, M, or V; Y196 replaced with F, or W; G197 replaced with A, I, L, S, T, M, or V; Q198 replaced with N; V199 replaced with A, G, I, L, S, T, or M; L200 replaced with A, G, I, S, T, M, or V; Y201 replaced with F, or W; T202 replaced with A, G, I, L, S, M, or V; D203 replaced with E; K204 replaced with H, or R; T205 replaced with A, G, I, L, S, M, or V; Y206 replaced with F, or W; A207 replaced with F, or W; A207 replaced with G, I, L, S, T, M, or V; M208 replaced with A, G, I, L, S, T, or V; G209 replaced with A, I, L, S, T, M, or V; K210 replaced with K, or R; L211 replaced with A, G, I, S, T, M, or V; I212 replaced with A, G, L, T, M, or V; Q213 replaced with N; R214 replaced with H, or K; K215 replaced with H or R; K216 replaced with H, or R; V217 replaced with A, G, I, L, S, T, or M; H218 replaced with K, or R; V219 replaced with A, G, I, L, S, T, or M; F220 replaced with W, or Y; G221 replaced with A, I, L, S, T, M, or V; D222 replaced with E; E223 replaced with D; L224 replaced with A, G, I, S, T, M, or V; S225 replaced with A, G, I, L, T, M, or V; L226 replaced with A, G, I, S, T, M, or V; V227 replaced with A, G, I, L, S, T, or M; T228 replaced with A, G, I, S, M, or V; L229 replaced with A, G, I, S, T, M, or V; F230 replaced with W, or Y; R231 replaced with H, or K; I233 replaced with A, G, L, S, T, M, or V; Q234 replaced with N; N235 replaced with Q; M236 replaced with A, G, I, L, S, T, or V; E238 replaced with D; T239 replaced with A, G, I, L, S, M, or V; L240 replaced with A, G, I, S, T, M, or V; N242 replaced with Q; N243 replaced with Q; S244 replaced with A, G, I, L, T, M, or V; Y246 replaced with F, or W; S247 replaced with A, G, I, L, T, M, or V; A248 replaced with G, I, L, S, T, M, or V; G249 replaced with A, I, L, S, T, M, or V; I250 replaced with A, G, L, S, T, M, or V; A251 replaced with G, I, L, S, T, M, or V; K252 replaced with H, or R; L253 replaced with A, G, I, S, T, M, or V; E254 replaced with D; E255 replaced with D; G256 replaced with A, I, L, S, T, M, or V; D257 replaced with E; E258 replaced with D; L259 replaced with A, G, I, S, T, M, or V; Q260 replaced with N; L261 replaced with A, G, I, S, T, M, or V; A262 replaced with G, I, L, S, T, M, or V; I263 replaced with A, G, L, S, T, M, or V; R265 replaced with H, or K; E266 replaced with D; N267 replaced with Q; A268 replaced with G, I, L, S, T, M, or V; Q269 replaced with N; I270 replaced

with A, G, L, S, T, M, or V; S271 replaced with A, G, I, L, T, M, or V; L272 replaced with A, G, S, T, M, or V; D273 replaced with E; G274 replaced with A, I, L, S, T, M, or V; D275 replaced with E; V276 replaced with A, G, I, L, S, T, or M; T277 replaced with A, G, I, L, S, M, or V; F278 replaced with W, or Y; F279 replaced with W, or Y; G280 replaced with A, I, L, S, T, M, or V; A281 replaced with G, I, L, S, T, M, or V; L282 replaced with A, G, I, S, T, M, or V; K283 replaced with H, or R; L284 replaced with A, G, I, S, T, M, or V; and/or 285 replaced with A, G, I, S, T, M, or V.

In another embodiment, site directed changes at the amino acid level of B Lymphocyte Stimulator can be made by replacing a particular amino acid with a conservative substitution. Antibodies of the present invention may bind B Lymphocyte Stimulator amino acid sequences containing conservative substitution mutations of the polypeptide of SEQ ID NO:3229 including: M1 replaced with A, G, I, L, S, T, or V; D2 replaced with E; D3 replaced with E; S4 replaced with A, G, I, L, T, M, or V; T5 replaced with A, G, I, L, S, M, or V; E6 replaced with D; R7 replaced with H, or K; E8 replaced with D; Q9 replaced with N; S10 replaced with A, G, I, L, T, M, or V; R11 replaced with H, or K; L12 replaced with A, G, I, S, T, M, or V; T13 replaced with A, G, I, L, S, M, or V; S14 replaced with A, G, I, L, M, or V; L16 replaced with A, G, I, S, T, M, or V; K17 replaced with H, or R; K18 replaced with H, or R; R19 replaced with H, or K; E20 replaced with D; E21 replaced with D; M22 replaced with A, G, I, L, S, T, or V; K23 replaced with H, or R; L24 replaced with A, G, I, S, T, M, or V; K25 replaced with H, or R; E26 replaced with D; V28 replaced with A, G, I, L, S, T, or M; S29 replaced with A, G, I, L, T, M, or V; I30 replaced with A, G, L, S, T, M, or V; L31 replaced with A, G, I, L, S, T, M, or V; R33 replaced with H, or K; K34 replaced with H, or R; E35 replaced with D; S36 replaced with A, G, I, L, T, M, or V; S38 replaced with A, G, I, L, T, M, or V; V39 replaced with A, G, I, L, S, T, or M; R40 replaced with K or K; S41 replaced with A, G, I, L, T, M, or V; S42 replaced with A, G, I, L, T, M, or V; K43 replaced with H, or R; D44 replaced with E; G45 replaced with A, I, L, S, T, M, or V; K46 replaced with H, or R; L47 replaced with A, G, I, S, T, M, or V; L48 replaced with A, G, I, L, S, T, M, or V; A49 replaced with G, I, L, S, T, M, or V; A50 replaced with G, L, I, S, T, M, or V; T51 replaced with A, G, I, L, S, M, or V; L52 replaced with A, G, I, S, T, M, or V; L53 replaced with A, G, I, S, T, M, or V; L54 replaced with A, G, I, S, T, M, or V; A55 placed with G, I, L, S, T, M, or V; L56 replaced with A, G, I, S, T, M, or V; L57 replaced with A, G, I, S, T, M, or V; S58 replaced with A, G, I, L, T, M, or V; L61 replaced with A, G, I, S, T, M, or V; T62 replaced with A, G, I, L, S, M, or V; V63 replaced with A, G, I, L, S, T, or M; V64 replaced with A, G, I, L, S, T, or M; S65 replaced with A, G, I, L, T, M, or V; F66 replaced with W, or Y; Y67 replaced with F, or W; Q68 replaced with N; V69 replaced with A, G, I, L, S, T, or M; A70 replaced with G, I, L, S, T, M, or V; A71 replaced with G, I, L, S, T, M, or V; L72 replaced with A, G, I, S, T, M, or V; Q73 replaced with N; G74 replaced with A, I, L, S, T, M, or V; D75 replaced with E; L76 replaced with A, G, I, S, T, M, or V; A77 replaced with G, I, L, S, T, M, or V; S78 replaced with A, G, I, L, T, M, or V; L79 replaced with A, G, I, S, T, M, or V; R80 replaced with H or K; A81 replaced with G, I, L, S, T, M, or V; E82 replaced with D; L83 replaced with A, G, I, S, T, M, or V; Q84 replaced with N; G85 replaced with A, I, L, S, T, M, or V; H86 replaced with K, or R; H87 replaced with K, or R; A88 replaced with G, I, L, S, T, M, or V; E89 replaced with D; K90 replaced with H or R; L91 replaced with A, G, I, S, T, M, or V; A93 replaced with G, I, L, S, T, M, or V; G94 replaced with A, I, L, S, T, M, or V; A95 replaced with G, I, L, S, T, M, or V; G96 replaced with A, I, L, S, T, M, or V; A97 replaced

with G, I, L, S, T, M, or V; K99 replaced with H or R; A100 replaced with G, I, L, S, T, M, or V; G101 replaced with A, I, L, S, T, M, or V; L102 replaced with A, G, I, S, T, M, or V; E103 replaced with D; E104 replaced with D; A105 replaced with G, I, L, S, T, M, or V; A107 replaced with G, I, L, S, T, M, or V; V108 replaced with A, G, I, L, S, T, or M; T109 replaced with A, G, I, L, S, M, or V; A110 replaced with G, I, L, S, T, M, or V; G111 replaced with A, I, L, S, T, M, or V; L112 replaced with A, G, I, S, T, M, or V; K113 replaced with H, or R; I114 replaced with A, G, L, S, T, M, or V; F115 replaced with W, or Y; E116 replaced with D; A119 replaced with G, I, L, S, T, M, or V; G121 replaced with A, I, L, S, T, M, or V; E122 replaced with D; G123 replaced with A, I, L, S, T, M, or V; N124 replaced with Q; S125 replaced with A, G, I, L, T, M, or V; S126 replaced with A, G, I, L, T, M, or V; Q127 replaced with N; N128 replaced with Q; S129 replaced with A, G, I, L, T, M, or V; R130 replaced with H, or K; N131 replaced with Q; K132 replaced with H, or R; R133 replaced with H, or K; A134 replaced with G, I, L, S, T, M, or V; V135 replaced with A, G, I, L, S, T, or M; Q136 replaced with N; G137 replaced with A, I, L, S, T, M, or V; E139 replaced with D; E140 replaced with D; T141 replaced with A, G, I, L, S, M, or V; G142 replaced with A, I, L, S, T, M, or V; S143 replaced with A, G, I, L, T, M, or V; Y144 replaced with F, or W; T145 replaced with A, G, I, L, S, M, or V; F146 replaced with W, or Y; V147 replaced with A, G, I, L, S, T, or M; W149 replaced with F, or Y; L150 replaced with A, G, I, S, T, M, or V; L151 replaced with A, G, I, S, T, M, or V; S152 replaced with A, G, I, L, T, M, or V; F153 replaced with W, or Y; K154 replaced with H, or R; R155 replaced with H, or K; G156 replaced with A, I, L, S, T, M, or V; S157 replaced with A, G, I, L, T, M, or V; A158 replaced with G, I, L, S, T, M, or V; L159 replaced with A, G, I, S, T, M, or V; E160 replaced with D; E161 replaced with D; K162 replaced with H, or R; E163 replaced with D; N164 replaced with Q; K165 replaced with H, or R; I166 replaced with A, G, L, S, T, M, or V; L167 replaced with A, G, I, S, T, M, or V; V168 replaced with A, G, I, L, S, T, or M; K169 replaced with H, or R; E170 replaced with D; T171 replaced with A, G, I, L, S, M, or V; G172 replaced with A, I, L, S, T, M, or V; Y173 replaced with F, or W; F174 replaced with W, or Y; F175 replaced with W, or Y; I176 replaced with A, G, I, L, S, T, M, or V; Y177 replaced with F, or W; G178 replaced with A, I, L, S, T, M, or V; Q179 replaced with N; V180 replaced with A, G, I, L, S, T, or M; L181 replaced with A, G, I, S, T, M, or V; Y182 replaced with F, or W; T183 replaced with A, G, I, L, S, M, or V; D184 replaced with E; K185 replaced with H, or R; T186 replaced with A, G, I, L, S, M, or V; Y187 replaced with F, or W; A188 replaced with G, I, L, S, T, M, or V; M189 replaced with A, G, I, L, S, T, or V; G190 replaced with A, I, L, S, T, M, or V; H191 replaced with K, or R; L192 replaced with A, G, I, S, T, M, or V; I193 replaced with A, G, L, S, T, M, or V; Q194 replaced with N; R195 replaced with H, or K; K196 replaced with H, or R; K197 replaced with H, or R; V198 replaced with A, G, I, L, S, T, or M; H199 replaced with K, or R; V200 replaced with A, G, I, L, S, T, or M; F201 replaced with W, or Y; G202 replaced with A, I, L, S, T, M, or V; D203 replaced with E; E204 replaced with D; L205 replaced with A, G, I, S, T, M, or V; S206 replaced with A, G, I, L, T, M, or V; T207 replaced with A, G, I, S, T, M, or V; V208 replaced with A, G, I, L, S, T, or M; T209 replaced with A, G, I, L, S, M, or V; L210 replaced with A, G, I, S, T, M, or V; F211 replaced with W, or Y; R212 replaced with H, or K; I214 replaced with A, G, L, S, T, M, or V; Q215 replaced with N; N216 replaced with Q; M217 replaced with A, G, I, L, S, T, or V; E219 replaced with D; T220 replaced with A, G, I, L, S, M, or V; L221 replaced with A, G, I, S, T, M, or V; N223 replaced with Q; N224 replaced

with Q; S225 replaced with A, G, I, L, T, M, or V; Y227 replaced with F, or W; S228 replaced with A, G, I, L, T, M, or V; A229 replaced with G, I, S, T, M, or V; G230 replaced with A, I, L, S, T, M, or V; I231 replaced with A, G, L, S, T, M, or V; A232 replaced with G, I, L, S, T, M, or V; K233 replaced with H, or R; L234 replaced with A, G, I, S, T, M, or V; E235 replaced with D; E236 replaced with D; G237 replaced with A, I, L, S, T, M, or V; D238 replaced with E; E239 replaced with D; L240 replaced with A, G, I, S, T, M, or V; Q241 replaced with N; L242 replaced with A, G, I, S, T, M, or V; A243 replaced with G, I, L, S, T, M, or V; L244 replaced with A, G, L, S, T, M, or V; R246 replaced with H, or K; E247 replaced with D; N248 replaced with Q; A249 replaced with G, I, L, S, T, M, or V; Q250 replaced with N; I251 replaced with A, G, L, S, T, M, or V; S252 replaced with A, G, I, L, T, M, or V; L253 replaced with A, G, I, S, T, M, or V; D254 replaced with E; G255 replaced with A, I, L, S, T, M, or V; D256 replaced with E; V257 replaced with A, G, I, L, S, T, or M; T258 replaced with A, G, I, L, S, M, or V; F259 replaced with W, or Y; F260 replaced with W, or Y; G261 replaced with A, I, L, S, T, M, or V; A262 replaced with G, I, L, S, T, M, or V; L263 replaced with A, G, I, S, T, M, or V; K264 replaced with H or R; L265 replaced with A, G, I, S, T, M, or V; and/or L266 replaced with A, G, I, S, T, M, or V.

In another embodiment, site directed changes at the amino acid level of B Lymphocyte Stimulator can be made by replacing a particular amino acid with a conservative substitution. Antibodies of the present invention may bind B Lymphocyte Stimulator amino acid sequences containing conservative substitution mutations of the polypeptide of any one of SEQ ID NOS:3230-3237.

Amino acids in the B Lymphocyte Stimulator polypeptides that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham and Wells, *Science* 244: 1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for functional activity, such as ligand binding and the ability to stimulate lymphocyte (e.g., B cell) as, for example, proliferation, differentiation, and/or activation. Accordingly, antibodies of the present invention may bind amino acids in the B Lymphocyte Stimulator polypeptides that are essential for function. In preferred embodiments, antibodies of the present invention bind amino acids in the B Lymphocyte Stimulator polypeptides that are essential for function and inhibit B Lymphocyte Stimulator polypeptide function. In other preferred embodiments, antibodies of the present invention bind amino acids in the B Lymphocyte Stimulator polypeptides that are essential for function and enhance B Lymphocyte Stimulator polypeptide function.

Of special interest are substitutions of charged amino acids with other charged or neutral amino acids which may produce proteins with highly desirable improved characteristics, such as less aggregation. Aggregation may not only reduce activity but also be problematic when preparing pharmaceutical formulations, because aggregates can be immunogenic (Pinckard et al., *Clin. Exp. Immunol.* 2:331-340 (1967); Robbins et al., *Diabetes* 36: 838-845 (1987); Cleland et al., *Crit. Rev. Therapeutic Drug Carrier Systems* 10:307-377 (1993)).

In another embodiment, the invention provides for antibodies that bind polypeptides having amino acid sequences containing non-conservative substitutions of the amino acid sequence provided in SEQ ID NO:3228. For example, non-conservative substitutions of the B Lymphocyte Stimulator protein sequence provided in SEQ ID NO:3228 include: M1 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D2 replaced

with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D3 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S4 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T5 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E6 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R7 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E8 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q9 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S10 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R11 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L12 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T13 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S14 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C15 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; L16 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K17 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K18 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R19 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E20 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E21 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; M22 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K23 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L24 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K25 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E26 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C27 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; V28 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S29 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I30 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L31 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P32 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; R33 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K34 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E35 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S36 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P37 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; S38 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V39 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R40 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S41 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S42 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K43 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D44 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G45 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K46 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L47 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L48 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A49 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A50 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T51 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L52 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L53 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L54 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A55 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L56 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L57 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S58 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C59 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; C60 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; L61 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T62 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V63 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V64 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S65 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F66 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or

W, Y, P, or C; Y196 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G197 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q198 replaced with D, E, H, K, R, A, G, I, S, T, M, V, F, W, Y, P, or C; V199 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L200 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y201 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T202 replaced with D, E, H, R, N, Q, F, W, Y, P, or C; D203 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K204 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T205 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y206 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; A207 replaced with D, E, H, Y, R, N, Q, F, W, Y, P, or C; M208 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G209 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H210 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L211 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I212 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q213 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; R214 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K215 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K216 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V217 replaced with D, E, H, V, R, N, Q, F, W, Y, P, or C; H218 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V219 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F220 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G221 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D222 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E223 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L224 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S225 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L226 replaced with D, E, H, R, N, Q, F, W, Y, P, or C; V227 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T228 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L229 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F230 replaced with D, E, F, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; R231 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C232 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I233 replaced with D, E, H, R, N, Q, F, W, Y, P, or C; Q234 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N235 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; M236 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P237 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E238 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T239 replaced with D, E, H, R, N, Q, F, W, Y, P, or C; L240 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P241 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N242 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N243 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S244 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C245 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Y246 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S247 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A248 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G249 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I250 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A251 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K252 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L253 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E254 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E255 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G256 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D257 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E258 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L259 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C;

Q260 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L261 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A262 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I263 replaced with D, E, H, R, N, Q, F, W, Y, P, or C; P264 replaced with D, E, H, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R265 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E266 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N267 replaced with D, E, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; A268 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q269 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; I270 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S271 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L272 replaced with D, E, H, R, N, Q, F, W, Y, P, or C; D273 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G274 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D275 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V276 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T77 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F278 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F279 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G280 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A281 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L282 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K283 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L284 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; and/or L285 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C.

In an additional embodiment, antibodies of the present invention bind B Lymphocyte Stimulator polypeptides comprising, or alternatively consisting of, a B Lymphocyte Stimulator amino acid sequence in which more than one amino acid (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30 and 50) is replaced with the substituted amino acids as described above (either conservative or nonconservative).

In another embodiment of the invention, antibodies of the present invention bind B Lymphocyte Stimulator polypeptides with non-conservative substitutions of the sequence provided in SEQ ID NO:3229 including: M1 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D2 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D3 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S4 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T5 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E6 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R7 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E8 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q9 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S10 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R11 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L12 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T13 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S14 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C15 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L16 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K17 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K18 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R19 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E20 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E21 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; M22 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; 23 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L24 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K25 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E26 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C27 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V28 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S29

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R, N, Q, F, W, Y, P, or C; G96 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A97 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P98 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K99 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A100 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G101 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L102 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E103 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E104 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A105 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P106 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A108 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V 108 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T109 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A110 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G111 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L112 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K113 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I114 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F15 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; E116 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P117 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; P118 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A119 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P120 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G121 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E122 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G123 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; N124 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S125 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S126 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q127 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N128 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S129 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R130 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N131 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K132 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R133 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V135 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q136 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G137 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P138 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E139 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E140 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T141 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G142 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S143 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y144 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T145 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F146 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; V147 replaced with D, E, K, R, N, Q, F, W, Y, P, or C; P148 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; W149 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; L150 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L151 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S152 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F153 replaced with D, E, H, Y, R, N, Q, A, G, I, L, S, T, M, V, P, or C; K154 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G156 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S157 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A158 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L159

replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E160 replaced with H, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E161 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K162 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E163 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N164 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; K165 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; I166 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L167 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V168 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K169 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E170 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T171 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G172 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y173 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F174 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F175 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; I176 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y177 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G178 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q179 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; V180 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L181 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y182 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; T183 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D184 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K185 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T186 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Y187 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; A188 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; M189 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G190 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H191 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L192 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I193 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q194 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; R195 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K196 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K197 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V198 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H199 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V200 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F201 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G202 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D203 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E204 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L205 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S206 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L207 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V208 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T209 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L210 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F211 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; R212 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C213 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or P; I214 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q215 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N216 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; M217 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P218 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E219 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; T220 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L221 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P222 replaced with D, E, H, K, R, A, G, I, L, S, T,

M, V, N, Q, F, W, Y, or C; N223 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; N224 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S225 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C226 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or P; Y227 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; S228 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A229 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; G230 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I231 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A232 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K233 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L234 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E235 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E236 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G237 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D238 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E239 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L240 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q241 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; L242 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A243 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I244 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P245 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R246 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E247 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; N248 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; A249 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q250 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; I251 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S252 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L253 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D254 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G255 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D256 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; V257 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T258 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F259 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; F260 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; G261 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A262 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L263 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K264 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L265 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; and/or L266 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C.

In another embodiment, site directed changes at the amino acid level of B Lymphocyte Stimulator can be made by replacing a particular amino acid with a non-conservative substitution. Antibodies of the present invention may bind B Lymphocyte Stimulator amino acid sequences containing non-conservative substitution mutations of the polypeptide of any one of SEQ ID NOS:3230-3237.

In an additional embodiment, antibodies of the present invention bind B Lymphocyte Stimulator polypeptides comprising, or alternatively consisting of, a B Lymphocyte Stimulator amino acid sequence in which more than one amino acid (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30 and 50) is replaced with the substituted amino acids as described above (either conservative or nonconservative).

Replacement of amino acids can also change the selectivity of the binding of a ligand to cell surface receptors. For example, Ostade et al., *Nature* 361:266-268 (1993) describes certain mutations resulting in selective binding of TNF-alpha to only one of the two known types of TNF receptors. Since B Lymphocyte Stimulator is a member of the TNF polypeptide

family, mutations similar to those in TNF- α are likely to have similar effects in B Lymphocyte Stimulator polypeptides.

Sites that are critical for ligand-receptor binding can also be determined by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith et al., *J. Mol. Biol.* 224:899-904 (1992) and de Vos et al. *Science* 255:306-312 (1992)).

Since B Lymphocyte Stimulator is a member of the TNF-related protein family, mutations may be made in sequences encoding amino acids in the TNF conserved domain, e.g., in positions Gly-191 through Leu-284 of SEQ ID NO:3228 or in positions Gly-172 through Leu-265 of SEQ ID NO:3229, may modulate rather than completely eliminate functional activities (e.g., biological activities) of B Lymphocyte Stimulator polypeptides or fragments or variants thereof. Accordingly, antibodies of the present invention may bind B Lymphocyte Stimulator polypeptides that have mutations in the TNF conserved domain and act as antagonists of B Lymphocyte Stimulator. In other preferred embodiments, antibodies of the present invention may bind B Lymphocyte Stimulator polypeptides that have mutations in the TNF conserved domain and act as agonists of B Lymphocyte Stimulator.

Recombinant DNA technology known to those skilled in the art (see, for instance, DNA shuffling supra) can be used to create novel mutant proteins or muteins including single or multiple amino acid substitutions, deletions, additions or fusion proteins. Such modified polypeptides can show, e.g., enhanced activity or increased stability. In addition, they may be purified in higher yields and show better solubility than the corresponding natural polypeptide, at least under certain purification and storage conditions.

Thus, the invention also encompasses antibodies that bind B Lymphocyte Stimulator derivatives and analogs that have one or more amino acid residues deleted, added, or substituted to generate B Lymphocyte Stimulator polypeptides, e.g., that are better suited for expression, scale up, etc., in the host cells. For example, cysteine residues can be deleted or substituted with another amino acid residue in order to eliminate disulfide bridges; N-linked glycosylation sites can be altered or eliminated to achieve, for example, expression of a homogeneous product that is more easily recovered and purified from yeast hosts which are known to hyperglycosylate N-linked sites. To this end, a variety of amino acid substitutions at one or both of the first or third amino acid positions on any one or more of the glycosylation recognition sequences in the B Lymphocyte Stimulator polypeptides of the invention, and/or an amino acid deletion at the second position of any one or more such recognition sequences will prevent glycosylation of the B Lymphocyte Stimulator at the modified tripeptide sequence (see, e.g., Miyajimo et al., *EMBO J* 5(6): 1193-1197). By way of non-limiting example, mutation of the serine at position 244 to alanine either singly or in combination with mutation of the asparagine at position 242 to glutamine abolishes glycosylation of the mature soluble form of B Lymphocyte Stimulator (e.g., amino acids 134-285 of SEQ ID NO:3228) when expressed in the yeast *Pichia pastoris*. A mutant B Lymphocyte Stimulator polypeptide in which only the asparagine at position 242 is mutated to glutamine, is still glycosylated when expressed in *Pichia pastoris*. In this mutant, the glycosylation event may be due to the activation or unmasking of an O-linked glycosylation site at serine 244. Similar mutations affecting glycosylation could also be made in the B Lymphocyte Stimulator polypeptide of

SEQ ID NO:3229, i.e., asparagine-223 to glutamine and/or serine-224 to alanine of SEQ ID NO:3229. Additionally, one or more of the amino acid residues of the polypeptides of the invention (e.g., arginine and lysine residues) may be deleted or substituted with another residue to eliminate undesired processing by proteases such as, for example, furins or kex-ins. One possible result of such a mutation is that B Lymphocyte Stimulator polypeptide of the invention is not cleaved and released from the cell surface. Accordingly, antibodies of the invention may bind B Lymphocyte Stimulator derivatives and analogs that have one or more amino acid residues deleted, added, or substituted. In other embodiments, antibodies of the invention may bind B Lymphocyte Stimulator derivatives, variants or analogs that are unable to be cleaved from the cell surface.

In a specific embodiment, antibodies of the invention bind B Lymphocyte Stimulator polypeptides in which Lys-132 and/or Arg-133 of the B Lymphocyte Stimulator sequence shown in SEQ ID NO:3228 is mutated to another amino acid residue, or deleted altogether, to prevent or diminish release of the soluble form of B Lymphocyte Stimulator from cells expressing B Lymphocyte Stimulator. In a more specific embodiment, antibodies of the invention bind B Lymphocyte Stimulator polypeptides in which Lys-132 of the B Lymphocyte Stimulator sequence shown in SEQ ID NO:3228 is mutated to Ala-132. In another, nonexclusive specific embodiment, antibodies of the invention bind B Lymphocyte Stimulator polypeptides in which Arg-133 of the B Lymphocyte Stimulator sequence shown in SEQ ID NO:3228 is mutated to Ala-133. These mutated proteins, and/or have uses such as, for example, in ex vivo therapy or gene therapy, to engineer cells expressing a B Lymphocyte Stimulator polypeptide that is retained on the surface of the engineered cells.

In a specific embodiment, antibodies of the invention bind B Lymphocyte Stimulator polypeptides in which Cys-146 of the B Lymphocyte Stimulator sequence shown in SEQ ID NO:3228 is mutated to another amino acid residue, or deleted altogether, for example, to aid preventing or diminishing oligomerization of the mutant B Lymphocyte Stimulator polypeptide when expressed in an expression system. In a specific embodiment, antibodies of the invention bind B Lymphocyte Stimulator polypeptides in which Cys-146 is replaced with a serine amino acid residue.

In another specific embodiment, antibodies of the invention bind B Lymphocyte Stimulator polypeptides in which Cys-232 of the B Lymphocyte Stimulator sequence shown in SEQ ID NO:3228 is mutated to another amino acid residue, or deleted altogether, for example, to aid preventing or diminishing oligomerization of the mutant B Lymphocyte Stimulator polypeptide when expressed in an expression system. In a specific embodiment, antibodies of the invention bind B Lymphocyte Stimulator polypeptides in which Cys-232 is replaced with a serine amino acid residue. Polypeptides encoding these polypeptides are also encompassed by the invention.

In yet another specific embodiment, antibodies of the invention bind B Lymphocyte Stimulator polypeptides in which Cys-245 of the B Lymphocyte Stimulator sequence shown in SEQ ID NO:3228 is mutated to another amino acid residue, or deleted altogether, for example, to aid preventing or diminishing oligomerization of the mutant B Lymphocyte Stimulator polypeptide when expressed in an expression system. In a specific embodiment, antibodies of the invention bind B Lymphocyte Stimulator polypeptides in which Cys-

245 is replaced with a serine amino acid residue. Polypeptides encoding these polypeptides are also encompassed by the invention.

The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of the B Lymphocyte Stimulator polypeptides can be substantially purified by the one-step method described in Smith and Johnson, *Gene* 67:31-40 (1988).

The antibodies of the present invention bind B Lymphocyte Stimulator polypeptides including the complete polypeptide encoded by the deposited cDNA (ATCCTM Deposit No. 97768) including the intracellular, transmembrane and extracellular domains of the polypeptide encoded by the deposited cDNA, the mature soluble polypeptide encoded by the deposited cDNA, the extracellular domain minus the intracellular and transmembrane domains of the protein, the complete polypeptide of SEQ ID NO:3228, the mature soluble polypeptide of SEQ ID NO:3228, e.g., amino acids 134-285 of SEQ ID NO:3228, the extracellular domain of SEQ ID NO:3228, amino acid residues 73-285 of SEQ ID NO:3228 minus the intracellular and transmembrane domains, as well as polypeptides which have at least 80%, 85%, 90% similarity, more preferably at least 95% similarity, and still more preferably at least 96%, 97%, 98% or 99% similarity to those described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

The antibodies of the present invention bind B Lymphocyte Stimulator polypeptides including the complete polypeptide encoded by the deposited cDNA including the intracellular, transmembrane and extracellular domains of the polypeptide encoded by the deposited cDNA (ATCCTM Deposit No. 203518), the mature soluble polypeptide encoded by the deposited cDNA, the extracellular domain minus the intracellular and transmembrane domains of the protein, the complete polypeptide of SEQ ID NO:3229, the mature soluble of SEQ ID NO:3229, e.g., amino acid residues 134-266 of SEQ ID NO:3229, the extracellular domain of SEQ ID NO:3229, e.g., amino acid residues 73-266 of SEQ ID NO:3229 minus the intracellular and transmembrane domains, as well as polypeptides which have at least 80%, 85%, 90% similarity, more preferably at least 95% similarity, and still more preferably at least 96%, 97%, 98% or 99% similarity to those described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Further antibodies of the present invention bind polypeptides including polypeptides at least 80%, or at least 85% identical, more preferably at least 90% or 95% identical, still more preferably at least 96%, 97%, 98% or 99% identical to the polypeptide encoded by the deposited cDNA (ATCCTM Deposit No. 97768) or to the polypeptide of SEQ ID NO:3228, and also include antibodies that bind portions of such polypeptides with at least 30 amino acids and more preferably at least 50 amino acids.

Further antibodies of the present invention bind polypeptides including polypeptides at least 80%, or at least 85% identical, more preferably at least 90% or 95% identical, still more preferably at least 96%, 97%, 98% or 99% identical to the polypeptide encoded by the deposited cDNA (ATCCTM Deposit No. 203518) or to the polypeptide of SEQ ID NO:3229, and also include antibodies that bind portions of such polypeptides with at least 30 amino acids and more preferably at least 50 amino acids. Polynucleotides encoding these polypeptides are also encompassed by the invention.

By "% similarity" for two polypeptides is intended a similarity score produced by comparing the amino acid sequences of the two polypeptides using the Bestfit program (Wisconsin

Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, Wis. 53711) and the default settings for determining similarity. Bestfit uses the local homology algorithm of Smith and Waterman (*Advances in Applied Mathematics* 2:482-489, 1981) to find the best segment of similarity between two sequences.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a reference amino acid sequence of a B Lymphocyte Stimulator polypeptide is intended that the amino acid sequence of the polypeptide is identical to the reference sequence except that the polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the reference amino acid of the B Lymphocyte Stimulator polypeptide. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a reference amino acid sequence, up to 5% of the amino acid residues in the reference sequence may be deleted or substituted with another amino acid, or a number of amino acids up to 5% of the total amino acid residues in the reference sequence may be inserted into the reference sequence. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence of SEQ ID NO:3228, the amino acid sequence encoded by the deposited cDNA clone HNEDU15 (ATCCTM Accession No. 97768), or fragments thereof, or, for instance, to the amino acid sequence of SEQ ID NO:3229, the amino acid sequence encoded by the deposited cDNA clone HDPMC52 (ATCCTM Accession No. 203518), or fragments thereof, can be determined conventionally using known computer programs such as the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, Wis. 53711). When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference amino acid sequence and that gaps in homology of up to 5% of the total number of amino acid residues in the reference sequence are allowed.

In a specific embodiment, the identity between a reference (query) sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, is determined using the FASTDB computer program based on the algorithm of Brutlag et al. (*Comp. App. Biosci.* 6:237-245 (1990)). Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter. According to this embodiment, if the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction is made to the results to take into consideration the fact that the FASTDB program does not account for N- and C-terminal truncations of the subject sequence, when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the

query sequence, the percent identity is connected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. A determination of whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of this embodiment. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence. For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C-termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are made for the purposes of this embodiment.

Antibodies that Immunospecifically Bind B Lymphocyte Stimulator Polypeptides

The present invention also encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to B Lymphocyte Stimulator polypeptides, which antibodies comprise, or alternatively consist of, all or a portion of a heavy and/or light chain variable domain of the scFvs referred to in Table 1.

The present invention also encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with aberrant B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor expression or inappropriate B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor function in an animal, preferably a mammal, and most preferably a human, comprising using antibodies (including molecules which comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to B Lymphocyte Stimulator. Diseases and disorders which can be detected, diagnosed or prognosed with the antibodies of the invention include, but are not limited to, immune disorders (e.g., lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (e.g., asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (e.g., AIDS), and proliferative disorders (e.g., leukemia, carcinoma, and lymphoma).

The present invention further encompasses methods and compositions for preventing, treating or ameliorating diseases or disorders associated with aberrant B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor expression or inappropriate B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor function in an animal, preferably a mammal, and most preferably a human, comprising administering to said animal an effective amount of one or more antibodies (including molecules which comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to B Lymphocyte Stimulator. Diseases and disorders which can be prevented, treated or inhibited by administering an effective amount of one or more antibodies or molecules of the invention include, but are not limited to, immune disorders (e.g., lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (e.g., asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (e.g., AIDS), and proliferative disorders (e.g., leukemia, carcinoma, and lymphoma).

Anti-B Lymphocyte Stimulator Antibodies

The antibodies of the present invention were discovered, in part, using phage display technology. Single chain antibody molecules ("scFvs") displayed on the surface of phage particles were screened to identify those scFvs that immunospecifically bind to B Lymphocyte Stimulator, including the membrane-bound form and soluble form of B Lymphocyte Stimulator. The present invention encompasses the scFvs and portions thereof that were identified to immunospecifically bind to B Lymphocyte Stimulator, including scFvs that immunospecifically bind to the soluble form of B Lymphocyte Stimulator, scFvs that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator, and scFvs that immunospecifically bind to both the soluble form and membrane-bound form of B Lymphocyte Stimulator. In particular, the present invention encompasses scFvs comprising, or alternatively consisting of, the amino acid sequence of SEQ ID NOS: 1-2128, as referred to in Table 1. Preferably, the scFvs of the present invention comprise, or alternatively consist of, the amino acid sequence of SEQ ID NOS: 1-46, 321-329, 834-872, 1563-1595, or 1881-1908. The scFvs include scFvs that bind to soluble B Lymphocyte Stimulator (e.g., scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1563-1880), scFvs that bind to the membrane-bound form of B Lymphocyte Stimulator (e.g., scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1881-2128), and scFvs that bind to both the soluble form and the membrane-bound form of B Lymphocyte Stimulator (e.g., scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1-1562). Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs, that immunospecifically bind to B Lymphocyte Stimulator are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

In one embodiment of the present invention, scFvs that immunospecifically bind to B Lymphocyte Stimulator comprise a polypeptide having the amino acid sequence of any one of the VH domains referred to in Table 1 and/or any one of the VL domains referred to in Table 1. In preferred embodiments, scFvs of the present invention comprise the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention comprise the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In another embodiment, scFvs that immunospe-

cifically bind to B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs referred to in Table 1 and/or any one, two, three, or more of the VL CDRs referred to in Table 1. In preferred embodiments, scFvs of the present invention comprise the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention comprise the amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. Molecules comprising, or alternatively consisting of, antibody fragments or variants of the scFvs referred to in Table 1 that immunospecifically bind to B Lymphocyte Stimulator are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

(Table 1 can be Found at the End of the Specification Just Prior to the Claims.)

In another embodiment of the present invention, an scFv that immunospecifically binds to a soluble form of B Lymphocyte Stimulator, comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS: 1563-1880 as referred to in Table 1. In a preferred embodiment, an scFv that immunospecifically binds to a soluble form of B Lymphocyte Stimulator comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS: 1570-1595. In an even more preferred embodiment, an scFv that immunospecifically binds to a soluble form of B Lymphocyte Stimulator comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS: 1563-1569.

In another embodiment of the present invention, an scFv that immunospecifically binds to a membrane-bound form of B Lymphocyte Stimulator comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS: 1881-2128 as referred to in Table 1. In a preferred embodiment, an scFv that immunospecifically binds to a membrane-bound form of B Lymphocyte Stimulator comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS: 1886-1908. In an even more preferred embodiment, an scFv that immunospecifically binds to a membrane-bound form of B Lymphocyte Stimulator comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS: 1881-1885.

In another embodiment of the present invention, an scFv that immunospecifically binds to both the soluble form and membrane-bound form of B Lymphocyte Stimulator comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS: 1-1562 as referred to in Table 1. In a preferred embodiment, an scFv that immunospecifically binds to both the soluble form and membrane-bound form of B Lymphocyte Stimulator comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS: 834-872. In another preferred embodiment, an scFv that immunospecifically binds to both the soluble form and membrane-bound form of B Lymphocyte Stimulator comprises, or alternatively consists of, any one of the amino acids sequences of SEQ ID NOS: 1-46 or 321-329. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs, that immunospecifically bind to the soluble form of B Lymphocyte Stimulator and/or the membrane-bound form of B Lymphocyte Stimulator are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

In another embodiment of the present invention, scFvs that immunospecifically bind to the soluble form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of any one of the VH domains contained in SEQ ID NOS: 1563-1880 as disclosed in Table 1 and/or any one of the VL domains contained in SEQ ID NOS: 1563-1880

as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of B Lymphocyte Stimulator, comprise a polypeptide having amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. In another embodiment, scFvs that immunospecifically bind to the soluble form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs SEQ ID NOS: 1563-1880 as disclosed in Table 1 and/or any one, two, three, or more of the VL CDRs contained in contained SEQ ID NOS: 1563-1880, as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In a preferred embodiment, scFvs that immunospecifically bind to the soluble form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of any one of the VH CDR3s contained in SEQ ID NOS: 1563-1880 as disclosed in Table 1 and/or any one of the VL CDR3s contained in SEQ ID NOS: 1563-1880 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs, that immunospecifically bind to B Lymphocyte Stimulator, preferably the soluble form of B Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

In another embodiment of the present invention, scFvs that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator comprise a polypeptide having the amino acid sequence of any one of the VH domains contained in SEQ ID NOS: 1881-2128 as disclosed in Table 1 and/or any one of the VL domains contained in SEQ ID NOS: 1881-2128 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In another embodiment, scFvs that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs contained in SEQ ID NOS: 1881-2128 as disclosed in Table 1 and/or any one, two, three, or more of

the VL CDRs contained in SEQ ID NOS: 1881-2128 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In a preferred embodiment, scFvs that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of any one of the VH CDR3s contained in SEQ ID NOS: 1881-2128 as disclosed in Table 1 and/or any one of the VL CDR3s contained in SEQ ID NOS: 1881-2128 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs, that immunospecifically bind to B Lymphocyte Stimulator, preferably the membrane-bound form of B Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

In another embodiment of the present invention, scFvs that immunospecifically bind to the soluble form and membrane-bound form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of any one of the VH domains contained in SEQ ID NOS: 1-1562 as disclosed in Table 1 and/or any one of the VL domains contained in SEQ ID NOS: 1-1562 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble and membrane-bound forms of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble form and membrane-bound form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In another embodiment, scFvs that immunospecifically bind to the soluble form and membrane-bound form of B Lymphocyte Stimulator comprise a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs contained in SEQ ID NOS: 1-1562 as disclosed in Table 1 and/or any one, two, three, or more of the VL CDRs contained in SEQ ID NOS: 1-1562 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble form and membrane-bound form of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble and membrane-bound forms of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In a preferred embodiment, scFvs that immu-

nospecifically bind to the soluble and membrane-bound forms of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of any one of the VH CDR3s contained in SEQ ID NOS: 1-1562 as disclosed in Table 1 and/or any one of the VL CDR3s contained in SEQ ID NOS: 1-1562, as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble and membrane-bound forms of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble and membrane-bound forms of B Lymphocyte Stimulator, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs or molecules, that immunospecifically bind to B Lymphocyte Stimulator, preferably the soluble and membrane-bound forms of B Lymphocyte Stimulator, are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

The present invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or a polypeptide fragment of B Lymphocyte Stimulator. In particular, the invention provides antibodies corresponding to the scFvs referred to in Table 1, such scFvs may routinely be "converted" to immunoglobulin molecules by inserting, for example, the nucleotide sequences encoding the VH and/or VL domains of the scFv into an expression vector containing the constant domain sequences and engineered to direct the expression of the immunoglobulin molecule, as described in more detail in Example 20, *infra*.

In one embodiment, the invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) wherein said antibodies comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one of the VH domains contained in the sequences referred to in Table 1. The present invention also provides antibodies that immunospecifically bind to a polypeptide, or polypeptide fragment of B Lymphocyte Stimulator, wherein said antibodies comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one, two, three, or more of the VH CDRs contained in the sequences referred to in Table 1. Molecules comprising, or alternatively consisting of, these antibodies, or antibody fragments or variants thereof, that immunospecifically bind to B Lymphocyte Stimulator or a B Lymphocyte Stimulator fragment are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments and/or variants.

In one embodiment of the present invention, antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind B Lymphocyte Stimulator, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH CDR referred to in Table 1. In particular, the invention provides antibodies that immunospecifically bind B Lymphocyte Stimulator, comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of a VH CDR1 contained in SEQ ID NOS: 1-46, 321-329, 1563-1569, or 1881-1885 as disclosed in Table 1. In another embodiment, antibodies that immunospecifically bind B Lymphocyte Stimulator, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH CDR2 contained in SEQ ID NOS: 1-46, 321-329, 1563-1569, or 1881-1885 as

disclosed in Table 1. In a preferred embodiment, antibodies that immunospecifically bind B Lymphocyte Stimulator, comprise, or alternatively consist of a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1-46, 321-329, 1563-1569, or 1881-1885 as disclosed in Table 1. In yet another embodiment, antibodies that immunospecifically bind B Lymphocyte Stimulator, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH CDR1 contained in SEQ ID NOS:834-872, 1570-1595, or 1886-1908 as disclosed in Table 1; a VH CDR2 contained in SEQ ID NOS: SEQ ID NOS: SEQ ID NOS:834-872, 1570-1595, or 1886-1908; and/or a VH CDR3 contained in SEQ ID NOS: SEQ ID NOS:834-872, 1570-1595, or 1886-1908 as disclosed in Table 1. Preferably, antibodies of the invention comprise, or alternatively consist of, VH CDRs that are derived from the same scFv as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies that immunospecifically bind to B Lymphocyte Stimulator are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

The present invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants) that immunospecifically bind to a polypeptide, or polypeptide fragment of B Lymphocyte Stimulator. In particular, the invention provides antibodies wherein said antibodies comprise, or alternatively consist of, a VL domain having an amino acid sequence of any one of the VL domains referred to in Table 1. The present invention also provides antibodies that immunospecifically bind to a polypeptide or polypeptide fragment of B Lymphocyte Stimulator, wherein said antibodies comprise, or alternatively consist of, a VL CDR having an amino acid sequence of any one, two, three, or more of the VL CDRs contained in the sequences referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies that immunospecifically bind to B Lymphocyte Stimulator are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

In one embodiment of the present invention, antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind B Lymphocyte Stimulator, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VL CDR referred to in Table 1. In particular, the invention provides antibodies that immunospecifically bind B Lymphocyte Stimulator, comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of a VL CDR1 contained in SEQ ID NOS:1-46, 321-329, 1563-1569, or 1881-1885 as disclosed in Table 1. In another embodiment, antibodies that immunospecifically bind B Lymphocyte Stimulator comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VL CDR2 contained in SEQ ID NOS:1-46, 321-329, 1563-1569, or 1881-1885 as disclosed in Table 1. In a preferred embodiment, antibodies comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VL CDR3 contained in SEQ ID NOS: in SEQ ID NOS:1-46, 321-329, 1563-1569, or 1881-1885 disclosed in Table 1. In yet another embodiment, antibodies that immunospecifically bind B Lymphocyte Stimulator comprise, or alternatively consist of: a polypeptide having the amino acid sequence of a VL CDR1 contained in SEQ ID NOS:834-872, 1570-1595, or 1886-1908 as disclosed in Table 1; a VL CDR2 SEQ ID NOS:834-872, 1570-1595, or 1886-1908 as disclosed in Table 1; and a VL CDR3 contained SEQ ID NOS:834-872, 1570-1595, or 1886-1908

as disclosed in Table 1. Preferably, antibodies of the invention comprise, or alternatively consist of, VL CDRs that are derived from the same scFv as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies, that immunospecifically bind to B Lymphocyte Stimulator are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

The present invention also provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or a polypeptide fragment of B Lymphocyte Stimulator, wherein said antibodies comprise, or alternatively consist of, a VH domain of one of the scFvs referred to in Table 1 combined with a VL domain of one of the scFvs referred to in Table 1, or other VL domain. The present invention further provides antibodies (including molecules comprising, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or a polypeptide fragment of B Lymphocyte Stimulator, wherein said antibodies comprise, or alternatively consist of, a VL domain of one of the scFvs referred to in Table 1 combined with a VR domain of one of the scFvs referred to in Table 1, or other VH domain. In a preferred embodiment, antibodies that immunospecifically bind to a polypeptide or a polypeptide fragment of B Lymphocyte Stimulator, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VH domain contained SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1 and a VL domain contained in contained SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1. In a further preferred embodiment, the antibodies of the invention comprise, or alternatively consist of, a VH and a VL domain from the same scFv as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies, that immunospecifically bind to B Lymphocyte Stimulator are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

The present invention also provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants) that immunospecifically bind to a polypeptide or polypeptide fragment of B Lymphocyte Stimulator, wherein said antibodies comprise, or alternatively consist of, one, two, three, or more VH CDRs and one, two, three or more VL CDRs, as referred to in Table 1. In particular, the invention provides for antibodies that immunospecifically bind to a polypeptide or polypeptide fragment of B Lymphocyte Stimulator, wherein said antibodies comprise, or alternatively consist of, a VH CDR1 and a VL CDR1, a VH CDR1 and a VL CDR2, a VH CDR1 and a VL CDR3, a VH CDR2 and a VL CDR1, VH CDR2 and VL CDR2, a VH CDR2 and a VL CDR3, a VH CDR3 and a VH CDR1, a VH CDR3 and a VL CDR2, a VH CDR3 and a VL CDR3, or any combination thereof, of the VR CDRs and VL CDRs referred to in Table 1. In a preferred embodiment, one or more of these combinations are from the same scFv as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies, that immunospecifically bind to B Lymphocyte Stimulator are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

In a preferred embodiment the invention provides antibodies wherein the VH CDRX (where X=1, 2, or 3) and VL CDRY (where Y=1, 2, or 3) are from scFvs with the same specificity (i.e., from scFvs that bind soluble B Lymphocyte

Stimulator, from scFvs that bind membrane-bound B Lymphocyte Stimulator, or from scFvs that bind both soluble and membrane-bound B Lymphocyte Stimulator. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies, that immunospecifically bind to B Lymphocyte Stimulator are also encompassed by the invention, as are nucleic acid molecules encoding these antibodies, molecules, fragments or variants.

The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. As such, the term "antibody" encompasses not only whole antibody molecules, but also antibody fragments, as well as variants (including derivatives) of antibodies and antibody fragments. Antibodies of the invention include, but are not limited to, monoclonal, multispecific, human or chimeric antibodies, single chain antibodies, single chain Fvs (scFvs), Fab fragments, F(ab')₂ fragments, Fd fragments, disulfide-linked Fvs (sdFvs), anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The immunoglobulin molecules of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG₁, IgG₂, IgG₃, IgG₄, IgA₁ and IgA₂) or subclass of immunoglobulin molecule. The antibodies of the present invention also include molecules comprising, or alternatively consisting of, a polypeptide having an amino acid sequence of a portion of an amino acid sequence contained SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908. Preferably, an antibody of the invention comprises, or alternatively consists of, a polypeptide having an amino acid sequence of a VH domain, VH CDR, VL domain, or VL CDR of any one those contained in the sequences referred to in Table 1. Antibodies of the invention also include molecules comprising, or alternatively consisting of, fragments or variants of the above antibodies that immunospecifically bind B Lymphocyte Stimulator.

Most preferably the antibodies of the present invention are whole antibodies or antibody fragments that immunospecifically bind human B Lymphocyte Stimulator. Antibody fragments of the invention that immunospecifically bind human B Lymphocyte Stimulator include, but are not limited to, Fab, Fab' and F(ab')₂, Fd fragments, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFvs), fragments comprising, or alternatively consisting of, either a VL or VH domain, and epitope binding fragments of any of the above.

B Lymphocyte Stimulator-binding antibody fragments, including single-chain antibodies, may comprise, or alternatively consist of, the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. In a preferred embodiment, the antibodies of the invention comprise, or alternatively consist of, a polypeptide that immunospecifically binds to B Lymphocyte Stimulator, said polypeptides comprise, or alternatively consist of, one, two, three, four, five, six or more CDRs referred to in Table 1, preferably a polypeptide having an amino acid sequence of a VH CDR3 and/or a VL CDR3 of contained SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1. Most preferably, antibodies of the invention comprise, or alternatively consist of, one, two, three, four, five, six or more CDRs from the same scFv, as referred to in Table 1. The antibodies of the invention may be from any animal origin, including birds and mammals. Preferably, the antibodies are human, murine (e.g., mouse and rat), donkey, sheep, rabbit, goat, guinea pig,

camel, horse, or chicken. Most preferably, the antibodies are human antibodies. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries and xenonice or other organisms that have been genetically engineered to produce human antibodies. For a detailed discussion of a few of the technologies for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent No. 0 598 877; U.S. Pat. Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; and 5,939,598; and Lonberg and Huszar, *Int. Rev. Immunol.* 13:65-93 (1995), which are incorporated by reference herein in their entirety. Human antibodies or "humanized" chimeric monoclonal antibodies can be produced using techniques described herein or otherwise known in the art. For example, methods for producing chimeric antibodies are known in the art. See, for review the following references which are hereby incorporated in their entirety: Morrison, *Science* 229:1202 (1985); Oi et al., *BioTechniques* 4:214 (1986); Cabilly et al., U.S. Pat. No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., *Nature* 312:643 (1984); Neuberger et al., *Nature* 314:268 (1985). In addition, companies such as Abgenix, Inc. (Fremont, Calif.) and Genpharm (San Jose, Calif.) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

The antibodies of the present invention may be monovalent, bivalent, trivalent or multivalent. For example, monovalent scFvs can be multimerized either chemically or by association with another protein or substance. An scFv that is fused to a hexahistidine tag or a Flag tag can be multimerized using Ni-NTA agarose (Qiagen) or using anti-Flag antibodies (Stratagene, Inc.).

The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a B Lymphocyte Stimulator polypeptide, or fragment thereof, or may be specific for both a B Lymphocyte Stimulator polypeptide, or fragment thereof, and a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, et al., *J. Immunol.* 147: 60-69 (1991); U.S. Pat. Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., *J. Immunol.* 148: 1547-1553 (1992).

The antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may bind immunospecifically to murine B Lymphocyte Stimulator (e.g., a polypeptide having the amino acid sequence of human B Lymphocyte Stimulator (SEQ ID NOS:3228 and/or 3229) or B Lymphocyte Stimulator expressed on human monocytes; murine B Lymphocyte Stimulator (SEQ ID NOS:3230 and/or 3231) or B Lymphocyte Stimulator expressed on murine monocytes; rat B Lymphocyte Stimulator (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form, e.g., on the surface of rat monocytes); or monkey B Lymphocyte Stimulator (e.g., the monkey B Lymphocyte Stimulator polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey B Lymphocyte Stimulator, or B Lymphocyte Stimulator expressed on monkey monocytes), preferably the antibodies of the invention bind immunospecifically to human B Lymphocyte Stimulator.

Preferably, the antibodies of the invention bind immunospecifically to human and monkey B Lymphocyte Stimulator. Also preferably, the antibodies of the invention bind immunospecifically to human B Lymphocyte Stimulator and murine B Lymphocyte Stimulator. More preferably, antibodies of the invention, bind immunospecifically and with higher affinity to human B Lymphocyte Stimulator than to murine B Lymphocyte Stimulator.

Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a polypeptide of the present invention are included. Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, antibodies of the present invention cross react with APRIL (SEQ ID NO:3239; GenBank Accession No. AF046888; J. Exp. Med. 188(6): 1185-1190; PCT International Publication WO97/33902). In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide of the present invention under hybridization conditions (as described herein).

In preferred embodiments, the antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), immunospecifically bind to B Lymphocyte Stimulator and do not cross-react with any other antigens. In more preferred embodiments, the antibodies of the invention immunospecifically bind to B Lymphocyte Stimulator and do not cross-react with TRAIL, APRIL, Endokine-alpha, TNF-alpha, TNF-beta, Fas-L or LIGHT.

The present invention also provides for a nucleic acid molecule, generally isolated, encoding an antibody of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof). In one embodiment, a nucleic acid molecule of the invention encodes an antibody comprising, or alternatively consisting of, a VH domain having an amino acid sequence of any one of the VH domains referred to in Table 1. In another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VH CDR1 having an amino acid sequence of any one of the VH CDR1s referred to in Table 1. In another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VH CDR2 having an amino acid sequence of any one of the VH CDR2s referred to in Table 1. In yet another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VH CDR3 having an amino acid sequence of any one of the VH

CDR3s referred to in Table 1. Nucleic acid molecules encoding antibodies that immunospecifically bind B Lymphocyte Stimulator and comprise, or alternatively consist of, fragments or variants of the VH domains and/or VH CDRs are also encompassed by the invention.

In another embodiment, a nucleic acid molecule of the invention encodes an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), comprising, or alternatively consisting of, a VL domain having an amino acid sequence of any one of the VL domains referred to in Table 1. In another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VL CDR1 having amino acid sequence of any one of the VL CDR1s referred to in Table 1. In another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VL CDR2 having an amino acid sequence of any one of the VL CDR2s referred to in Table 1. In yet another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VL CDR3 having an amino acid sequence of any one of the VL CDR3s referred to in Table 1. Nucleic acid encoding antibodies that immunospecifically bind B Lymphocyte Stimulator and comprise, or alternatively consist of, fragments or variants of the VL domains and/or VLCDR(s) are also encompassed by the invention.

In another embodiment, a nucleic acid molecule of the invention encodes an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), comprising, or alternatively consisting of, a VH domain having an amino acid sequence of any one of the VH domains referred to in Table 1 and a VL domain having an amino acid sequence of any one of the VL domains referred to in Table 1. In another embodiment, a nucleic acid molecule of the invention encodes an antibody comprising, or alternatively consisting of, a VH CDR1, a VL CDR1, a VH CDR2, a VL CDR2, a VH CDR3, a VL CDR3, or any combination thereof having an amino acid sequence referred to in Table 1. Nucleic acid encoding antibodies that immunospecifically bind B Lymphocyte Stimulator and comprise, or alternatively consist of, fragments or variants of the VL and/or domains and/or VHCDR(s) and/or VLCDR(s) are also encompassed by the invention.

The present invention also provides antibodies that comprise, or alternatively consist of, variants (including derivatives) of the VH domains, VH CDRs, VL domains, and VL CDRs described herein, which antibodies immunospecifically bind to B Lymphocyte Stimulator. Standard techniques known to those of skill in the art can be used to introduce mutations in the nucleotide sequence encoding a molecule of the invention, including, for example, site-directed mutagenesis and PCR-mediated mutagenesis which result in amino acid substitutions. Preferably, the variants (including derivatives) encode less than 50 amino acid substitutions, less than 40 amino acid substitutions, less than 30 amino acid substitutions, less than 25 amino acid substitutions, less than 20 amino acid substitutions, less than 15 amino acid substitutions, less than 10 amino acid substitutions, less than 5 amino acid substitutions, less than 4 amino acid substitutions, less than 3 amino acid substitutions, or less than 2 amino acid substitutions relative to the reference VH domain, VHCDR1, VHCDR2, VHCDR3, VL domain, VLCDR1, VLCDR2, or VLCDR3. In specific embodiments, the variants encode substitutions of VHCDR3. In a preferred embodiment, the variants have conservative amino acid substitutions at one or more predicted non-essential amino acid residues. A "conser-

vative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a side chain with a similar charge. Families of amino acid residues having side chains with similar charges have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for biological activity to identify mutants that retain activity (e.g., the ability to bind B Lymphocyte Stimulator). Following mutagenesis, the encoded protein may routinely be expressed and the functional and/or biological activity of the encoded protein, (e.g., ability to immunospecifically bind B Lymphocyte Stimulator) can be determined using techniques described herein or by routinely modifying techniques known in the art.

The antibodies of the invention include derivatives (i.e., variants) that are modified, e.g., by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not affect the ability of the antibody to immunospecifically bind to B Lymphocyte Stimulator. For example, but not by way of limitation, derivatives of the invention include antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to, specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

In a specific embodiment, an antibody of the invention (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), that immunospecifically binds B Lymphocyte Stimulator, comprises, or alternatively consists of, an amino acid sequence encoded by a nucleotide sequence that hybridizes to a nucleotide sequence that is complementary to that encoding one of the VH or VL domains referred to in Table 1 under stringent conditions, e.g., hybridization to filter-bound DNA in 6x sodium chloride/sodium citrate (SSC) at about 45° C. followed by one or more washes in 0.2xSSC/0.1% SDS at about 50-65° C., under highly stringent conditions, e.g., hybridization to filter-bound nucleic acid in 6xSSC at about 45° C. followed by one or more washes in 0.1xSSC/0.2% SDS at about 68° C., or under other stringent hybridization conditions which are known to those of skill in the art (see, for example, Ausubel, F. M. et al., eds., 1989, *Current Protocols in Molecular Biology*, Vol. 1, Green Publishing Associates, Inc. and John Wiley & Sons, Inc., New York at pages 6.3.1-6.3.6 and 2.10.3). In another embodiment, an antibody of the invention that immunospecifically binds to B Lymphocyte Stimulator, comprises, or alternatively consists of, an amino acid sequence encoded by a nucleotide sequence that hybridizes to a nucleotide sequence that is complementary to that encoding one of the VH CDRs or VL CDRs referred to in Table 1 under stringent conditions, e.g., hybridization under conditions as described above, or under other stringent hybridization conditions which are known to those of skill in the art. In another

embodiment, an antibody of the invention that immunospecifically binds to B Lymphocyte Stimulator, comprises, or alternatively consists of, an amino acid sequence encoded by a nucleotide sequence that hybridizes to a nucleotide sequence that is complementary to that encoding one of the VH CDR3s referred to in Table 1 under stringent conditions e.g., hybridization under conditions as described above, or under other stringent hybridization conditions which are known to those of skill in the art. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

In another embodiment, an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), that immunospecifically binds to B Lymphocyte Stimulator comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VH domains referred to in Table 1. In another embodiment, an antibody of the invention that immunospecifically binds to B Lymphocyte Stimulator comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VH CDRs referred to in Table 1. In another embodiment, an antibody of the invention that immunospecifically binds to B Lymphocyte Stimulator comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VH CDR3s referred to in Table 1. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

In another embodiment, an antibody of the invention (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), that immunospecifically binds to B Lymphocyte Stimulator comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VL domains referred to in Table 1. In another embodiment, an antibody of the invention that immunospecifically binds to B Lymphocyte Stimulator comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VL CDRs referred to in Table 1. In another embodiment, an antibody of the invention that immunospecifically binds to B Lymphocyte Stimulator comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VL CDR3s referred to in Table 1. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

Antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may also be described or specified

in terms of their binding affinity for to B Lymphocyte Stimulator polypeptides or fragments or variants of B Lymphocyte Stimulator polypeptides (e.g., to the soluble form of B Lymphocyte Stimulator polypeptides and/or membrane-bound form of B Lymphocyte Stimulator). In specific embodiments, antibodies of the invention bind B Lymphocyte Stimulator polypeptides, or fragments or variants thereof, with a dissociation constant or K_D of less than or equal to 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, or 10^{-5} M. More preferably, antibodies of the invention bind B Lymphocyte Stimulator polypeptides or fragments or variants thereof with a dissociation constant or K_D less than or equal to 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, or 10^{-8} M. Even more preferably, antibodies of the invention bind B Lymphocyte Stimulator polypeptides or fragments or variants thereof with a dissociation constant or K_D less than or equal to 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, or 10^{-15} M. The invention encompasses antibodies that bind B Lymphocyte Stimulator polypeptides with a dissociation constant or K_D that is within any one of the ranges that are between each of the individual recited values.

In specific embodiments, antibodies of the invention bind B Lymphocyte Stimulator polypeptides or fragments or variants thereof with an off rate (k_{off}) of less than or equal to 5×10^{-2} sec $^{-1}$, 10^{-2} sec $^{-1}$, 5×10^{-3} sec $^{-1}$ or 10^{-3} sec $^{-1}$. More preferably, antibodies of the invention bind B Lymphocyte Stimulator polypeptides or fragments or variants thereof with an off rate (k_{off}) less than or equal to 5×10^{-4} sec $^{-1}$, 10^{-4} sec $^{-1}$, 5×10^{-5} sec $^{-1}$, or 10^{-5} sec $^{-1}$. The invention encompasses antibodies that bind B Lymphocyte Stimulator polypeptides with an off rate (k_{off}) that is within any one of the ranges that are between each of the individual recited values.

In other embodiments, antibodies of the invention bind B Lymphocyte Stimulator polypeptides or fragments or variants thereof with an on rate (k_{on}) of greater than or equal to 10^3 M $^{-1}$ sec $^{-1}$, 5×10^3 M $^{-1}$ sec $^{-1}$, 10^4 M $^{-1}$ sec $^{-1}$ or 5×10^4 M $^{-1}$ sec $^{-1}$. More preferably, antibodies of the invention bind B Lymphocyte Stimulator polypeptides or fragments or variants thereof with an on rate (k_{on}) greater than or equal to 10^5 M $^{-1}$ sec $^{-1}$, 5×10^5 M $^{-1}$ sec $^{-1}$, 10^6 M $^{-1}$ sec $^{-1}$, or 5×10^6 M $^{-1}$ sec $^{-1}$. The invention encompasses antibodies that bind B Lymphocyte Stimulator polypeptides with on rate (k_{on}) that is within any one of the ranges that are between each of the individual recited values.

The invention also encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that have one or more of the same biological characteristics as one or more of the antibodies described herein. By "biological characteristics" is meant, the in vitro or in vivo activities or properties of the antibodies, such as, for example, the ability to bind to B Lymphocyte Stimulator (e.g., the soluble form of B Lymphocyte Stimulator, the membrane-bound form of B Lymphocyte Stimulator, the soluble form and membrane-bound form of B Lymphocyte Stimulator), and/or an antigenic and/or epitope region of B Lymphocyte Stimulator, the ability to substantially block B Lymphocyte Stimulator/B Lymphocyte Stimulator receptor (e.g., TACI-GenBank accession number AAC51790 and/or BCMA-GenBank accession number NP_001183) binding, or the ability to block B Lymphocyte Stimulator mediated biological activity (e.g., stimulation of B cell proliferation and immunoglobulin production). Optionally, the antibodies of the invention will bind to the same

epitope as at least one of the antibodies specifically referred to herein. Such epitope binding can be routinely determined using assays known in the art.

The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that neutralize B Lymphocyte Stimulator or a fragment thereof, said antibodies comprising, or alternatively consisting of, a portion (i.e., a VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, or VL CDR3) of an scFv referred to in Table 1, more preferably having an amino acid sequence contained in SEQ ID NOS:834-872, 1570-1595, or 1886-1908, and even more preferably having an amino acid sequence contained in SEQ ID NOS:1-46, 321-329, 1563-1569, or 1881-1885 as disclosed in Table 1, or a fragment or variant thereof. By an antibody that "neutralizes B Lymphocyte Stimulator or a fragment thereof" is meant an antibody that diminishes or abolishes the ability of B Lymphocyte Stimulator to bind to its receptor (e.g., TACI and BCMA) to stimulate B cell proliferation, to stimulate immunoglobulin secretion by B cells, and/or to stimulate the B Lymphocyte Stimulator receptor signalling cascade. In one embodiment, an antibody that neutralizes B Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that neutralizes B Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that neutralizes B Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR domain in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In a preferred embodiment, an antibody that neutralizes B Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that neutralizes B Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR domain contained in SEQ ID NOS: 1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In another preferred embodiment, an antibody that neutralizes B Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR3 contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that inhibit (i.e., diminish or abolish) B Lymphocyte Stimulator mediated B cell proliferation as determined by any method known in the art such as, for example, the assays described in Examples 21 and 22; infra, said antibodies comprising, or alternatively consisting of, a portion (e.g., a VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, or VL CDR3) of an

scFv having an amino acid sequence SEQ ID NOS:834-872, 1570-1595, 1886-1908, and even more preferably having an amino acid sequence SEQ ID NOS:1-46, 321-329, 1563-1569, 1881-1885 as disclosed in Table 1 or a fragment or variant thereof. In one embodiment, an antibody that inhibits B Lymphocyte Stimulator mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908, as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that inhibits B Lymphocyte Stimulator mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In a preferred embodiment, an antibody that inhibits B Lymphocyte Stimulator mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In another preferred embodiment, an antibody that inhibits B Lymphocyte Stimulator mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR3 contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that enhance the activity of B Lymphocyte Stimulator or a fragment thereof, said antibodies comprising, or alternatively consisting of, a portion (i.e., a VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, or VL CDR3) of an scFv having an amino acid sequence SEQ ID NOS:834-872, 1570-1595, or 1886-1908, and preferably having an amino acid sequence of SEQ ID NOS:1-46, 321-329, 1563-1569, or 1881-1885, as disclosed in Table 1, or a fragment or variant thereof. By an antibody that "enhances the activity of B Lymphocyte Stimulator or a fragment thereof" is meant an antibody increases the ability of B Lymphocyte Stimulator to bind to its receptor (e.g., TACI or BCMA), to stimulate B cell proliferation, to stimulate immunoglobulin secretion by B cells, and/or to stimulate the B Lymphocyte Stimulator receptor signalling cascade. In one embodiment, an antibody that enhances the activity of B Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that enhances the activity of B Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In a preferred embodiment, an antibody that enhances the activity of B Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of,

a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that enhances B Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR domain contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In another preferred embodiment, an antibody that enhances the activity of B Lymphocyte Stimulator or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR3 contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that stimulate B Lymphocyte Stimulator mediated B cell proliferation as determined by any method known in the art, such as, for example, the assays described in Examples 21 and 22, *infra*, said antibodies comprising, or alternatively consisting of, a portion (e.g., a VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, or VL CDR3) of an scFv having an amino acid sequence of SEQ ID NOS:834-872, 1570-1595, or 1886-1908, and even more preferably having an amino acid sequence of SEQ ID NOS:1-46, 321-329, 1563-1569, or 1881-1885 as disclosed in Table 1 or a fragment or variant thereof. In one embodiment, an antibody that stimulates B Lymphocyte Stimulator mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that stimulates B Lymphocyte Stimulator mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In a preferred embodiment, an antibody that stimulates B Lymphocyte Stimulator mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. In another preferred embodiment, an antibody that stimulates B Lymphocyte Stimulator mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR3 contained in SEQ ID NOS:1-46, 321-329, 834-872, 1563-1595, or 1881-1908 as disclosed in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

The present invention also provides for fusion proteins comprising, or alternatively consisting of, an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that immunospecifically binds to B Lymphocyte Stimulator, and a heterologous polypeptide. Preferably, the heterologous polypeptide to which the antibody is fused to is useful for B-cell function or is useful to target the antibody to B-cells. In an alternative preferred embodiment, the heterologous polypeptide to which the antibody is fused to is useful for monocyte cell function or is useful to target the antibody to a monocyte. In

another embodiment, the heterologous polypeptide to which the antibody is fused is albumin (including but not limited to recombinant human serum albumin or fragments or variants thereof (see, e.g., U.S. Pat. No. 5,876,969, issued Mar. 2, 1999, EP Patent 0 413 622, and U.S. Pat. No. 5,766,883, issued Jun. 16, 1998, herein incorporated by reference in their entirety)). In a preferred embodiment, antibodies of the present invention (including fragments or variants thereof) are fused with the mature form of human serum albumin (i.e., amino acids 1-585 of human serum albumin as shown in FIGS. 1 and 2 of EP Patent 0 322 094) which is herein incorporated by reference in its entirety. In another preferred embodiment, antibodies of the present invention (including fragments or variants thereof) are fused with polypeptide fragments comprising, or alternatively consisting of, amino acid residues 1-x of human serum albumin, where x is an integer from 1 to 585 and the albumin fragment has human serum albumin activity. In another preferred embodiment, antibodies of the present invention (including fragments or variants thereof) are fused with polypeptide fragments comprising, or alternatively consisting of amino acid residues 1-z of human serum albumin, where z is an integer from 369 to 419, as described in U.S. Pat. No. 5,766,883 herein incorporated by reference in its entirety. Antibodies of the present invention (including fragments or variants thereof) may be fused to either the N- or C-terminal end of the heterologous protein (e.g., immunoglobulin Fc polypeptide or human serum albumin polypeptide).

In one embodiment, a fusion protein of the invention comprises, or alternatively consists of, a polypeptide having the amino acid sequence of any one or more of the VH domains referred to in Table 1 or the amino acid sequence of any one or more of the VL domains referred to in Table 1 or fragments or variants thereof, and a heterologous polypeptide sequence. In another embodiment, a fusion protein of the present invention comprises, or alternatively consists of, a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs referred to in Table 1, or the amino acid sequence of any one, two, three, or more of the VL CDRs referred to in Table 1, or fragments or variants thereof, and a heterologous polypeptide sequence. In a preferred embodiment, the fusion protein comprises, or alternatively consists of, a polypeptide having the amino acid sequence of, a VH CDR3 referred to in Table 1, or fragment or variant thereof, and a heterologous polypeptide sequence, which fusion protein immunospecifically binds to B Lymphocyte Stimulator. In another embodiment, a fusion protein comprises, or alternatively consists of a polypeptide having the amino acid sequence of at least one VH domain referred to in Table 1 and the amino acid sequence of at least one VL domain referred to in Table 1 or fragments or variants thereof, and a heterologous polypeptide sequence. Preferably, the VH and VL domains of the fusion protein correspond to the same scFv referred to in Table 1. In yet another embodiment, a fusion protein of the invention comprises, or alternatively consists of a polypeptide having the amino acid sequence of any one, two, three or more of the VH CDRs referred to in Table 1 and the amino acid sequence of any one, two, three or more of the VL CDRs referred to in Table 1, or fragments or variants thereof, and a heterologous polypeptide sequence. Preferably, two, three, four, five, six, or more of the VH CDR(s) or VL CDR(s) correspond to the same scFv referred to in Table 1. Nucleic acid molecules encoding these fusion proteins are also encompassed by the invention.

The present invention also provides: antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that immunospecifically

bind to the soluble form of B Lymphocyte Stimulator-antibodies that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator, and antibodies that immunospecifically bind to both the soluble form and membrane-bound form of B Lymphocyte Stimulator.

In one embodiment of the present invention, antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to the soluble form of B Lymphocyte Stimulator, comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS: 1563-1880 as disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS: 1563-1880 as disclosed in Table 1, or fragment(s) or variant(s) (including derivative) thereof. Preferably, the VH and VL domains of the antibody correspond to the same scFv as disclosed in Table 1. In another embodiment, antibodies that immunospecifically bind to the soluble form of B Lymphocyte Stimulator are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs contained in SEQ ID NOS: 1563-1880 as disclosed in Table 1 and/or the amino acid sequence of any one, two, three, or more of the VL CDRs contained in SEQ ID NOS: 1563-1880 as disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, two, three, four, five, six or more of the VH and VL CDRs of the antibody correspond to the same scFv as disclosed in Table 1. In a preferred embodiment, antibodies that immunospecifically bind to the soluble form of B Lymphocyte Stimulator are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH CDR3s contained in SEQ ID NOS: 1563-1880 as disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS: 1563-1880 as disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, the VH CDR3 and VL CDR3 of the antibody correspond to the same scFv, as disclosed in Table 1. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

In another embodiment of the present invention, antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS: 1881-2128 as disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS: 1881-2128 as disclosed in Table 1, or a fragment or variant thereof. Preferably, the VH and VL domains of the antibody correspond to the same scFv as disclosed in Table 1. In another embodiment, antibodies that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs contained in SEQ ID NOS: 1881-2128 as disclosed in Table 1 and/or the amino acid sequence of any one, two, three, or more of the VL CDRs contained in SEQ ID NOS: 1881-2128 as disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, two, three, four, five, six or more of the VH and VL CDRs of the antibody correspond to the same scFv as disclosed in Table 1. In a preferred embodiment, antibodies that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or

more of the VH CDR3s contained in SEQ ID NOS: 1881-2128 as disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS: 1881-2128 as disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, the VHCDR3 and VLCDR3 of the antibody correspond to the same scFv, as disclosed in Table 1. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

In another embodiment of the present invention, antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to the soluble form and membrane-bound form of B Lymphocyte Stimulator, are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS: 1-1562 as disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS: 1-1562 as disclosed in Table 1, or a fragment or variant thereof. Preferably, the VH and VL domains of the antibody correspond to the same scFv as disclosed in Table 1. In another embodiment, antibodies that immunospecifically bind to the soluble form and membrane-bound form of B Lymphocyte Stimulator are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs contained in SEQ ID NOS: 1-1562 as disclosed in Table 1 and/or the amino acid sequence of any one, two, three, or more of the VL CDRs contained in SEQ ID NOS: 1-1562 as disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, two, three, four, five, six or more of the VH and VL CDRs of the antibody correspond to the same scFv as disclosed in Table 1. In a preferred embodiment, antibodies that immunospecifically bind to the soluble form and membrane-bound form of B Lymphocyte Stimulator are provided that comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one or more of the VH CDR3s contained in SEQ ID NOS: 1-1562, disclosed in Table 1 and/or the amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS: 1-1562, disclosed in Table 1, or fragment(s) or variant(s) thereof. Preferably, the VHCDR3 and VLCDR3 of the antibody correspond to the same scFv, as disclosed in Table 1.

The present invention also provides for mixtures of antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to B Lymphocyte Stimulator, wherein the mixture has at least one, two, three, four, five or more different antibodies of the invention. In particular, the invention provides for mixtures of different antibodies that immunospecifically bind to the soluble form of B Lymphocyte Stimulator, the membrane-bound form of B Lymphocyte Stimulator, and/or both the membrane-bound form and soluble form of B Lymphocyte Stimulator. In specific embodiments, the invention provides mixtures of at least 2, preferably at least 4, at least 6, at least 8, at least 10, at least 12, at least 15, at least 20, or at least 25 different antibodies that immunospecifically bind to B Lymphocyte Stimulator, wherein at least 1, at least 2, at least 4, at least 6, or at least 10, antibodies of the mixture is an antibody of the invention. In a specific embodiment, each antibody of the mixture is an antibody of the invention.

The present invention also provides for panels of antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to B Lymphocyte Stimulator, wherein the panel has at least one, two, three, four, five or more different antibodies of the invention. In particu-

lar, the invention provides for panels of different antibodies that immunospecifically bind to the soluble form of B Lymphocyte Stimulator, the membrane-bound form of B Lymphocyte Stimulator, and/or both the membrane-bound form and soluble form of B Lymphocyte Stimulator. In specific embodiments, the invention provides for panels of antibodies that have different affinities for B Lymphocyte Stimulator, different specificities for B Lymphocyte Stimulator, or different dissociation rates. The invention provides panels of at least 10, preferably at least 25, at least 50, at least 75, at least 100, at least 125, at least 150, at least 175, at least 200, at least 250, at least 300, at least 350, at least 400, at least 450, at least 500, at least 550, at least 600, at least 650, at least 700, at least 750, at least 800, at least 850, at least 900, at least 950, or at least 1000, antibodies. Panels of antibodies can be used, for example, in 96 well plates for assays such as ELISAs.

The present invention further provides for compositions comprising, one or more antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants of the invention). In one embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS: 1563-1880 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR1s contained in SEQ ID NOS: 1563-1880 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR2s contained in SEQ ID NOS: 1563-1880 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR3s contained in SEQ ID NOS: 1563-1880, as disclosed in Table 1 or a variant thereof.

The present invention further provides for compositions comprising, one or more antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants of the invention). In one embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS: 1881-2128 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR1s contained in SEQ ID NOS: 1881-2128 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR2s contained in SEQ ID NOS: 1881-2128 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or

more of the VH CDR3s contained in SEQ ID NOS: 1881-2128 as disclosed in Table 1 or a variant thereof.

The present invention further provides for compositions comprising, one or more antibodies (including scFvs, or molecules comprising, or alternatively consisting of antibody fragments or variants of the invention). In one embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH domains contained in SEQ ID NOS:1-1562 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR1s contained in SEQ ID NOS:1-1562 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR2s contained in SEQ ID NOS:1-1562 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH CDR3s contained in SEQ ID NOS:1-1562 as disclosed in Table 1 or a variant thereof.

Other embodiments of the present invention providing for compositions comprising, one or more antibodies (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the invention) are listed below. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS: 1563-1880 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR1s contained in SEQ ID NOS:1563-1880 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR2s contained in SEQ ID NOS: 1563-1880 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS:1563-1880 as disclosed in Table 1, or a variant thereof.

Other embodiments of the present invention providing for compositions comprising, one or more antibodies (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the invention) are listed below. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS:1881-2128 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that

comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR1s contained in SEQ ID NOS:1881-2128 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR2s SEQ ID NOS:1881-2128 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS:1881-2128 as disclosed in Table 1, or a variant thereof.

Other embodiments of the present invention providing for compositions comprising, one or more antibodies (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the invention) are listed below. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL domains contained in SEQ ID NOS:1-1562 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR1s contained in SEQ ID NOS:1-1562 as disclosed in Table 1, or a variant thereof. In another embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR2s SEQ ID NOS:1-1562 as disclosed in Table 1, or a variant thereof. In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VL CDR3s contained in SEQ ID NOS:1-1562 as disclosed in Table 1, or a variant thereof.

In a preferred embodiment, a composition of the present invention comprises, one, two, three, four, five, or more antibodies that comprise, or alternatively consist of, a polypeptide having an amino acid sequence of any one or more of the VH domains in disclosed in Table 1, or a variant thereof, and an amino acid sequence of any one or more of the VL domains disclosed in Table 1, or a variant thereof wherein the VH and VL domains are from scFvs with the same specificity (i.e., from scFvs that bind soluble B Lymphocyte Stimulator (SEQ ID NOS: 1563-1880), from scFvs that bind membrane-bound B Lymphocyte Stimulator (SEQ ID 1881-2128), or from scFvs that bind both soluble and membrane-bound B Lymphocyte Stimulator (SEQ ID NOS:1-1562). In a preferred embodiment the invention provides antibodies wherein the VH CDRX (where X=1,2, or 3) and VL CDRY (where Y=1,2, or 3) are from scFvs with the same specificity (i.e., from scFvs that bind soluble B Lymphocyte Stimulator (SEQ ID NOS: 1563-1880), from scFvs that bind membrane-bound B Lymphocyte Stimulator (SEQ ID NOS:1881-2128), or from scFvs that bind both soluble and membrane-bound B Lymphocyte Stimulator (SEQ ID NOS:1-1562). In yet another embodiment, a composition of the present invention comprises one or more fusion proteins.

As discussed in more detail below, a composition of the invention may be used either alone or in combination with other compositions. The antibodies (including scFvs and

other molecules comprising, or alternatively consisting of antibody fragments or variants of the present invention) may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalently and non-covalently conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Pat. No. 5,314,995; and EP 396,387.

Antibodies of the present invention (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the present invention) may be used, for example, but not limited to, to purify and detect B Lymphocyte Stimulator, and to target the polypeptides of the present invention to cells expressing membrane-bound B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor, including both in vitro and in vivo diagnostic and therapeutic methods. For example, the antibodies have use in immunoassays for qualitatively and quantitatively measuring levels of B Lymphocyte Stimulator in biological samples. See, e.g., Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988) (incorporated by reference herein in its entirety).

Methods Producing Antibodies

The antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of antibody fragments or variants of the invention) can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques.

The single chain Fvs disclosed in Table 1 were generated using phage display methods known in the art. Furthermore, other scFvs that immunospecifically bind B Lymphocyte Stimulator may be generated using phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In particular, DNA sequences encoding VH and VL domains are amplified from animal cDNA libraries (e.g., human or murine cDNA libraries of lymphoid tissues) or synthetic cDNA libraries. The DNA encoding the VH and VL domains are joined together by an scFv linker by PCR and cloned into a phagemid vector (e.g., p CANTAB 6 or pComb 3 HSS). The vector is electroporated in *E. coli* and the *E. coli* is infected with helper phage. Phage used in these methods are typically filamentous phage including fd and M 13 and the VH and VL domains are usually recombinantly fused to either the phage gene III or gene VIII. Phage expressing an antigen binding domain that binds to an antigen of interest (i.e., B Lymphocyte Stimulator or a fragment thereof) can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Examples of phage display methods that can be used to make the antibodies of the present invention include, but are not limited to, those disclosed in Brinkman et al., *J. Immunol. Methods* 182:41-50 (1995); Ames et al., *J. Immunol. Methods* 184:177-186 (1995); Kettleborough et al., *Eur. J. Immunol.* 24:952-958 (1994); Persic et al., *Gene* 187 9-18 (1997); Burton et al., *Advances in Immunology* 57:191-280(1994); PCT application No. PCT/GB91/01 134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/1 1236; WO 95/15982; WO 95/20401; WO97/13844; and U.S. Pat. Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717;

5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described below. Techniques to recombinantly produce Fab, Fab' and F(ab')₂ fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., *BioTechniques* 12(6):864-869 (1992); Sawai et al., *AJRI* 34:26-34 (1995); and Better et al., *Science* 240:1041-1043 (1988) (said references incorporated by reference in their entireties).

To generate whole antibodies, PCR primers including VH or VL nucleotide sequences, a restriction site, and a flanking sequence to protect the restriction site can be used to amplify the VH or VL sequences in scFv clones. Utilizing cloning techniques known to those of skill in the art, the PCR amplified VH domains can be cloned into vectors expressing a VH constant region, e.g., the human gamma 4 constant region, and the PCR amplified VL domains can be cloned into vectors expressing a VL constant region, e.g., human kappa or lambda constant regions. Preferably, the vectors for expressing the VH or VL domains comprise a promoter suitable to direct expression of the heavy and light chains in the chosen expression system, a secretion signal, a cloning site for the immunoglobulin variable domain, immunoglobulin constant domains, and a selection marker such as neomycin. The VH and VL domains may also be cloned into one vector expressing the necessary constant regions. The heavy chain conversion vectors and light chain conversion vectors are then co-transfected into cell lines to generate stable or transient cell lines that express full-length antibodies, e.g., IgG, using techniques known to those of skill in the art.

Cell lines that express antibodies that comprise the VH and VL domains of scFvs of the invention have been deposited with the American Type Culture Collection ("ATCC™") on the dates listed in Table 2 and given the ATCC™ Deposit Numbers identified in Table 2. The American Type Culture Collection is located at 10801 University Boulevard, Manassas, Va. 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganism for purposes of patent procedure.

Cell Line	Corresponding scFv	SEQ ID NO:	ATCC™	ATCC™
			Deposit	Deposit
			Number	Date
NSO-B11-15	I050B11-15	24	PTA-3238	Mar. 27, 2001
NSO-anti-BlyS-6D08-18	I006D08	2	PTA-3239	Mar. 27, 2001
NSO-anti-BlySB Lymphocyte Stimulator-116A01-60	I116A01	327	PTA-3240	Mar. 27, 2001
I026C04K	I026C04-K	1563	PTA-3241	Mar. 27, 2001
I050A12	I050A12	12	PTA-3242	Mar. 27, 2001
I050-B11	I050B11	9	PTA-3243	Mar. 27, 2001

Accordingly, in one embodiment, the invention provides antibodies that comprise the VH and VL domains of scFvs of the invention.

In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line NSO-B11-15.

In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line NSO-anti-BLyS-6D08-18.

In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line NSO-anti-BLyS-116A01-60.

In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line IO26C04K.

In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line IO50A12.

In a preferred embodiment, an antibody of the invention is the antibody expressed by cell line NSO-B11.

In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a B Lymphocyte Stimulator polypeptide. In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a B Lymphocyte Stimulator polypeptide by between 1% and 10% in a competitive inhibition assay. In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a B Lymphocyte Stimulator polypeptide by between 1% and 10% in a competitive inhibition assay.

In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a B Lymphocyte Stimulator polypeptide by at least 10% and up to 20% in a competitive inhibition assay.

In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a B Lymphocyte Stimulator polypeptide by at least 20% and up to 30% in a competitive inhibition assay.

In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a B Lymphocyte Stimulator polypeptide by at least 30% and up to 40% in a competitive inhibition assay.

In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a B Lymphocyte Stimulator polypeptide by at least 40% and up to 50% in a competitive inhibition assay.

In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or

variant of an scFv referred to in Table 1 to a B Lymphocyte Stimulator polypeptide by at least 50% and up to 60% in a competitive inhibition assay.

In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a B Lymphocyte Stimulator polypeptide by at least 60% and up to 70% in a competitive inhibition assay.

In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a B Lymphocyte Stimulator polypeptide by at least 70% and up to 80% in a competitive inhibition assay.

In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a B Lymphocyte Stimulator polypeptide by at least 80% and up to 90% in a competitive inhibition assay.

In preferred embodiments, the invention provides antibodies that which reduce the binding of an antibody comprising a fragment (e.g., VH domain, VL domain, VHCDR1, VHCDR2, VHCDR3, VLCDR1, VLCDR2, or VLCDR3) or variant of an scFv referred to in Table 1 to a B Lymphocyte Stimulator polypeptide by at least 90% and up to 100% in a competitive inhibition assay.

In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCCTM deposit number PTA-3238 to a B Lymphocyte Stimulator polypeptide.

In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCCTM deposit number PTA-3239 to a B Lymphocyte Stimulator polypeptide.

In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCCTM deposit number PTA-3240 to a B Lymphocyte Stimulator polypeptide.

In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCCTM deposit number PTA-3241 to a B Lymphocyte Stimulator polypeptide.

In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCCTM deposit number PTA-3242 to a B Lymphocyte Stimulator polypeptide.

In other preferred embodiments, the invention provides antibodies that competitively inhibit binding of the antibody produced by the cell line having ATCCTM deposit number PTA-3243 to a B Lymphocyte Stimulator polypeptide.

For some uses, including in vivo use of antibodies in humans and in vitro detection assays, it may be preferable to use human or chimeric antibodies. Completely human antibodies are particularly desirable for therapeutic treatment of human patients. See also, U.S. Pat. Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO98/16654, WO 96/34096, WO 96/33735, and WO 91/1 0741; each of which is incorporated herein by reference in its entirety. In a specific embodiment, antibodies of the present invention comprise one or more VH and VL domains corresponding to the human scFvs of the invention and framework regions from another immunoglobulin mol-

ecule, preferably a human immunoglobulin molecule. In a specific embodiment, antibodies of the present invention comprise one or more CDRs corresponding to the human scFvs of the invention and framework regions from another immunoglobulin molecule, preferably a human immunoglobulin molecule. In other embodiments, an antibody of the present invention comprises one, two, three, four, five, six or more VL CDRs or VH CDRs corresponding to one or more of the human scFvs referred to in Table 1, or fragments or variants thereof, and framework regions (and, optionally CDRs not derived from the scFvs in Table 1) from a human immunoglobulin molecule. In a preferred embodiment, an antibody of the present invention comprises a VH CDR3, VL CDR3, or both, corresponding to the same scFv, or different scFvs referred to in Table 1, or fragments or variants thereof, and framework regions from a human immunoglobulin.

A chimeric antibody is a molecule in which different portions of the antibody are derived from different immunoglobulin molecules such as antibodies having a variable region derived from a human antibody and a non-human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, *Science* 229:1202 (1985); Oi et al., *BioTechniques* 4:214 (1986); Gillies et al., *J. Immunol. Methods* 125:191-202 (1989); U.S. Pat. Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entirety. Chimeric antibodies comprising one or more CDRs from human species and framework regions from a non-human immunoglobulin molecule (e.g., framework regions from a canine or feline immunoglobulin molecule) can be produced using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Pat. Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, *Molecular Immunology* 28(4/5):489498 (1991); Studnicka et al., *Protein Engineering* 7(6):805-814 (1994); Roguska et al., *PNAS* 91:969-973 (1994)), and chain shuffling (U.S. Pat. No. 5,565,332). In a preferred embodiment, chimeric antibodies comprise a human CDR3 having an amino acid sequence of any one of the VH CDR3s or VL CDR3s referred to in Table 1, or a variant thereof, and non-human framework regions or human framework regions different from those of the frameworks in the corresponding scFv disclosed in Table 1. Often, framework residues in the framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Pat. No. 5,585,089; Riechmann et al., *Nature* 332:323 (1988), which are incorporated herein by reference in their entirety.)

Further, the antibodies of the invention can, in turn, be utilized to generate anti-idiotypic antibodies that "mimic" B Lymphocyte Stimulator polypeptides using techniques well known to those skilled in the art. (See, e.g., Greenspan & Bona, *FASEB J.* 7(5):437444 (1993); and Nissinoff, *J. Immunol.* 147(8):2429-2438 (1991)). For example, antibodies of the invention which bind to B Lymphocyte Stimulator and competitively inhibit the binding of B Lymphocyte Stimulator to its receptor (as determined by assays well known in the art such as, for example, that disclosed, *infra*) can be used to generate anti-idiotypes that "mimic" a B Lymphocyte Stimulator ligand/receptor-binding domain and, as a consequence, bind to and neutralize B Lymphocyte Stimulator receptors

(e.g., TACI BCMA, and TR20). Such neutralizing anti-idiotypes (including molecules comprising, or alternatively consisting of, antibody fragments or variants, such as Fab fragments of such anti-idiotypes) can be used in therapeutic regimens to neutralize B Lymphocyte Stimulator. For example, such anti-idiotypic antibodies can be used to bind B Lymphocyte Stimulator ligands/receptors, and thereby block B Lymphocyte Stimulator mediated biological activity. Alternatively, anti-idiotypes that "mimic" a B Lymphocyte Stimulator binding domain may bind to B Lymphocyte Stimulator receptor(s) and induce B Lymphocyte Stimulator receptor mediated signalling (e.g., activation of nuclear factor of activated T cells (NF-AT), nuclear factor-kappa B (NF-kappa B), and/or AP-1). Such agonistic anti-idiotypes (including agonistic Fab fragments of these anti-idiotypes) can be used in therapeutic regimens to induce or enhance B Lymphocyte Stimulator receptor mediated signalling. For example, such anti-idiotypic antibodies can be used to bind B Lymphocyte Stimulator ligands/receptors, and thereby stimulate B Lymphocyte Stimulator mediated biological activity (e.g., B cell proliferation and/or immunoglobulin production).

Once an antibody molecule of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) has been chemically synthesized or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, or more generally, a protein molecule, such as, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. Further, the antibodies of the present invention may be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

Polynucleotides Encoding an Antibody

The invention provides polynucleotides comprising, or alternatively consisting of, a nucleotide sequence encoding an antibody of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof). The invention also encompasses polynucleotides that hybridize under high stringency, or alternatively, under intermediate or lower stringency hybridization conditions, e.g., as defined *supra*, to polynucleotides complementary to nucleic acids having a polynucleotide sequence that encodes an antibody of the invention or a fragment or variant thereof.

The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. Since the amino acid sequences of the scFv antibodies and VH domains, VL domains and CDRs thereof, are known (as described in Table 1), nucleotide sequences encoding these antibodies can be determined using methods well known in the art, e., the nucleotide codons known to encode the particular amino acids are assembled in such a way to generate a nucleic acid that encodes the antibody, of the invention. Such a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., *BioTechniques* 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

Alternatively, a polynucleotide encoding an antibody (including molecules comprising, or alternatively consisting of,

antibody fragments or variants thereof) may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art

Once the nucleotide sequence of the antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, *Molecular Cloning, A Laboratory Manual*, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. and Ausubel et al., eds., 1998, *Current Protocols in Molecular Biology*, John Wiley & Sons, NY, which are both incorporated by reference herein in their entirety) to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

In a specific embodiment, one or more of the VH and VL domains referred to in Table 1, or fragments or variants thereof, is inserted within framework regions using recombinant DNA techniques known in the art. In a specific embodiment, one, two, three, four, five, six, or more of the CDRs referred to in Table 1, or fragments or variants thereof, is inserted within framework regions using recombinant DNA techniques known in the art. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., *J. Mol. Biol.* 278: 457-479 (1998) for a listing of human framework regions, the contents of which are hereby incorporated by reference in its entirety). Preferably, the polynucleotides generated by the combination of the framework regions and CDRs encode an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that specifically binds to B Lymphocyte Stimulator. Preferably, as discussed supra, polynucleotides encoding variants of antibodies or antibody fragments having one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules, or antibody fragments or variants, lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and fall within the ordinary skill of the art.

Recombinant Expression of an Antibody

Recombinant expression of an antibody of the invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof

(e.g., a heavy or light chain of an antibody of the invention or a portion thereof or a single chain antibody of the invention)), requires construction of an expression vector(s) containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule (e.g., a whole antibody, a heavy or light chain of an antibody, or portion thereof (preferably, but not necessarily, containing the heavy or light chain variable domain)), of the invention has been obtained, the vector(s) for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention (e.g., a whole antibody, a heavy or light chain of an antibody, a heavy or light chain variable domain of an antibody, or a portion thereof, or a heavy or light chain CDR, a single chain Fv, or fragments or variants thereof), operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Pat. No. 5,122,464, the contents of each of which are hereby incorporated by reference in its entirety) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy chain, the entire light chain, or both the entire heavy and light chains.

The expression vector(s) is(are) transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing polynucleotide(s) encoding an antibody of the invention (e.g., whole antibody, a heavy or light chain thereof, or portion thereof, or a single chain antibody of the invention, or a fragment or variant thereof), operably linked to a heterologous promoter. In preferred embodiments, for the expression of entire antibody molecules, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention in situ. These include, but are not limited to, microorganisms such as bacteria (e.g., *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3

cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter, the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as *Escherichia coli*, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., Gene 45:101 (1986); Cockett et al., Bio/Technology 8:2 (1990)).

In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited to, the *E. coli* expression vector pUR278 (Ruther et al., EMBO 1.2: 1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, Nucleic Acids Res. 13:3101-3109 (1985); Van Heeke & Schuster, J. Biol. Chem. 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

In an insect system, *Autographia californica* nuclear polyhedrosis virus (AcNPV) may be used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. Antibody coding sequences may be cloned individually into nonessential regions (for example, the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example, the polyhedrin promoter).

In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by in vitro or in vivo recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts (e.g., see Logan & Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see, e.g., Bittner et al., Methods in Enzymol. 153:51-544 (1987)).

In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include, but are not limited to, CHO, VERY, BHK, Hela, COS, NSO, MDCK, 293, 3T3, W138, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and HsS78Bst.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compositions that interact directly or indirectly with the antibody molecule.

A number of selection systems may be used, including but not limited to, the herpes simplex virus thymidine kinase (Wigler et al., Cell 11:223 (1977)), hypoxanthineguanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., Cell 22:817 (1980)) genes can be employed in tk-, hgpRT- or apt- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., Natl. Acad. Sci. USA 77:357 (1980); O'Hare et al., Proc. Natl. Acad. Sci. USA 78:1527 (1981)); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, Proc. Natl. Acad. Sci. USA 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 (Clinical Pharmacy 12:488-505; Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260: 926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62: 191-217 (1993); TIB TECH 11(5):155-215 (May, 1993)); and hygR, which confers resistance to hygromycin (Santerre et al., Gene 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-

Garapin et al., J. Mol. Biol. 150:1 (1981), which are incorporated by reference herein in their entireties.

The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol. 3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the coding sequence of the antibody, production of the antibody will also increase (Crouse et al., Mol. Cell. Biol. 3:257 (1983)).

The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain is preferably placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, Nature 322:52 (1986); Kohler, Proc. Natl. Acad. Sci. USA 77:2 197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

Once an antibody molecule of the invention has been produced by recombinant expression, it may be purified by any method known in the art for purification of an immunoglobulin molecule, or more generally, for purification of a protein, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. Further, the antibodies of the present invention may be fused to heterologous polypeptide sequences described herein or otherwise known in the art to facilitate purification.

Antibody Characterization

Antibodies of the present invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be characterized in a variety of ways. In particular, antibodies and related molecules of the invention may be assayed for the ability to immunospecifically bind to B Lymphocyte Stimulator or a fragment of B Lymphocyte Stimulator (e.g., to the soluble form or the membrane-bound form of B Lymphocyte Stimulator) using techniques described herein or routinely modifying techniques known in the art. B Lymphocyte Stimulator or B Lymphocyte Stimulator fragments that may be immunospecifically bound by the compositions of the invention include, but are not limited to, human B Lymphocyte Stimulator (SEQ ID NOS:3228 and/or 3229) or B Lymphocyte Stimulator expressed on human monocytes; murine B Lymphocyte Stimulator (SEQ ID NOS:3230 and/or 3231) or B Lymphocyte Stimulator expressed on murine monocytes; rat B Lymphocyte Stimulator (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form, e.g., on the surface of rat monocytes); or monkey B Lymphocyte Stimulator (e.g., the monkey B Lymphocyte Stimulator polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey B Lymphocyte Stimulator, or B Lymphocyte Stimulator expressed on monkey monocytes) or fragments thereof. Preferably compositions of the invention bind human B Lymphocyte Stimulator

(SEQ ID NOS:3228 and/or 3229) or fragments thereof. Assays for the ability of the antibodies of the invention to immunospecifically bind B Lymphocyte Stimulator or a fragment of B Lymphocyte Stimulator may be performed in solution (e.g., Houghten, Bio/Techniques 13:412421(1992)), on beads (e.g., Lam, Nature 354:82-84 (1991)), on chips (e.g., Fodor, Nature 364:555-556 (1993)), on bacteria (e.g., U.S. Pat. No. 5,223,409), on spores (e.g., U.S. Pat. Nos. 5,571,698; 5,403,484; and 5,223,409), on plasmids (e.g., Cull et al., Proc. Natl. Acad. Sci. USA 89:1865-1869 (1992)) or on phage (e.g., Scott and Smith, Science 249:386-390 (1990); Devlin, Science 249:404406 (1990); Cwirla et al., Proc. Natl. Acad. Sci. USA 87:6378-6382 (1990); and Felici, J. Mol. Biol. 222:301-310 (1991)) (each of these references is incorporated herein in its entirety by reference). Antibodies that have been identified to immunospecifically bind to B Lymphocyte Stimulator or a fragment of B Lymphocyte Stimulator can then be assayed for their specificity and affinity for B Lymphocyte Stimulator or a fragment of B Lymphocyte Stimulator using or routinely modifying techniques described herein or otherwise known in the art.

The antibodies of the invention may be assayed for immunospecific binding to B Lymphocyte Stimulator and cross-reactivity with other antigens by any method known in the art. In particular, the ability of an antibody to immunospecifically bind to the soluble form or membrane-bound form of B Lymphocyte Stimulator and the specificity of the antibody, fragment, or variant for B Lymphocyte Stimulator polypeptide from a particular species (e.g., murine, monkey or human, preferably human) may be determined using or routinely modifying techniques described herein or otherwise known in art.

Immunoassays which can be used to analyze immunospecific binding and cross-reactivity include, but are not limited to, competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasyolol) supplemented with protein phosphatase and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1 to 4 hours) at 40 degrees C., adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 40 degrees C., washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e.g., pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, e.g., Ausubel

et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%-20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e.g. PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e.g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e.g., an anti-human antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e.g., ^{32}P or ^{251}I) diluted in locking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

ELISAs comprise preparing antigen, coating the well of a 96-well microtiter plate with the antigen, washing away antigen that did not bind the wells, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) to the wells and incubating for a period of time, washing away unbound antibodies or non-specifically bound antibodies, and detecting the presence of the antibodies specifically bound to the antigen coating the well. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, the detectable molecule could be the antigen conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase). One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

The binding affinity of an antibody (including an scFv or other molecule comprising, or alternatively consisting of, antibody fragments or variants thereof) to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g., ^3H or ^{251}I) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of the present invention for B Lymphocyte Stimulator and the binding off-rates can be determined from the data by Scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, B Lymphocyte Stimulator is incubated with an antibody of the present invention conjugated to a labeled compound (e.g., ^3H or ^{125}I) in the presence of increasing amounts of an unlabeled second anti-B Lymphocyte Stimulator antibody.

In a preferred embodiment, BIAcore kinetic analysis is used to determine the binding on and off rates of antibodies (including an scFv or other molecule comprising, or alternatively consisting of, antibody fragments or variants thereof) to B Lymphocyte Stimulator, or fragments of B Lymphocyte Stimulator. BIAcore kinetic analysis comprises analyzing the binding and dissociation of B Lymphocyte Stimulator from chips with immobilized antibodies on their surface as described in detail in Examples 6, 12, 17 and 18, *infra*.

The antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) can also be assayed for their ability to inhibit, increase, or not significantly alter, the binding of B Lymphocyte Stimulator to a B Lymphocyte Stimulator receptor (e.g., TACI and BCMA) using techniques known to those of skill in the art. For example, cells expressing a receptor for B Lymphocyte Stimulator (e.g., IM9, REK, ARH-77 cells, Namalwa, and RPMI-8226 B cell tumor lines as well as peripheral CD20+ B cells) can be contacted with B Lymphocyte Stimulator in the presence or absence of an antibody, and the ability of the antibody to inhibit, increase, or not significantly alter, B Lymphocyte Stimulator binding to the cells can be measured. B Lymphocyte Stimulator binding to cells can be measured by, for example, flow cytometry or a scintillation assay. B Lymphocyte Stimulator or the antibody can be labeled with a detectable compound such as a radioactive label (e.g., ^{32}P , ^{35}S , and ^{125}I) or a fluorescent label (e.g., fluorescein isothiocyanate, rhodamine, phycoerythrin, phycoerythrin, allophycocyanin, g-phthaldehyde and fluorescein) to enable detection of an interaction between B Lymphocyte Stimulator and a B Lymphocyte Stimulator receptor and/or B Lymphocyte Stimulator and an antibody of the invention. Alternatively, the ability of antibodies of the invention to inhibit, increase, or not significantly alter, B Lymphocyte Stimulator binding to a B Lymphocyte Stimulator receptor can be determined in cell-free assays. For example, native or recombinant B Lymphocyte Stimulator (e.g., that having the amino acid sequence of amino acids 134-285 of SEQ ID NO:3228) or a fragment thereof can be contacted with an antibody and the ability of the antibody to inhibit, increase, or not significantly alter, B Lymphocyte Stimulator from binding to a B Lymphocyte Stimulator receptor can be determined. Preferably, the antibody is immobilized on a solid support and B Lymphocyte Stimulator or a B Lymphocyte Stimulator fragment is labeled with a detectable compound. Alternatively, B Lymphocyte Stimulator or a B Lymphocyte Stimulator fragment is immobilized on a solid support and the antibody is labeled with a detectable compound. B Lymphocyte Stimulator may be partially or completely purified (e.g. partially or completely free of other polypeptides) or part of a cell lysate. Further, the B Lymphocyte Stimulator polypeptide may be a fusion protein comprising B Lymphocyte Stimulator or a biologically active portion thereof and a domain such as an Immunoglobulin Fc or glutathione-S-transferase. For example, amino acid residues 1-154 of TACI (GenBank accession number AAC51790), or 1-48 of BCMA (GenBank accession number NP_001183) may be fused to the Fc region of an IgG molecule and used in a cell free assay to determine the ability of antibodies of the invention to inhibit, increase, or not significantly alter, B Lymphocyte Stimulator binding to a B Lymphocyte Stimulator receptor. Alternatively, B Lymphocyte Stimulator can be biotinylated using techniques well known to those of skill in the art (e.g., biotinylation kit, Pierce Chemicals; Rockford, Ill.).

The antibodies of the invention (including scFvs or other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), can also be assayed for

their ability to inhibit, stimulate, or not significantly alter, B Lymphocyte Stimulator-induced B-cell proliferation using techniques known to those of skill in the art. For example, B-cell proliferation can be assayed by ^3H -thymidine incorporation assays and trypan blue cell counts (see, e.g., Moore et al., *Science* 285: 260-263 (1999)). Further, the antibodies of the invention, or fragments or variants thereof, can be assayed for their ability to block, stimulate, or not significantly alter, B Lymphocyte Stimulator-induced activation of cellular signaling molecules and transcription factors such as calcium-modulator and cyclophilin ligand ("CAML"), calcineurin, nuclear factor of activated T cells transcription factor ("NF-AT"), nuclear factor-kappa B ("NF-kappa B"), and AP-1 using techniques known to those of skill in the art (see, e.g., von Bulow and Brat, *Science* 278:138-141(1997)). For example, NF-AT activity can be determined by electromobility gel shift assays, by detecting the expression of a protein known to be regulated by NF-AT (e.g., IL-2 expression), by detecting the induction of a reporter gene (e.g., an NF-AT regulatory element operably linked to a nucleic acid encoding a detectable marker such as luciferase, beta-galactosidase or chloramphenicol acetyltransferase (CAT)), or by detecting a cellular response (e.g., cellular differentiation, or cell proliferation).

The antibodies of the invention, or fragments or variants thereof can also be assayed for their ability to neutralize, enhance, or not significantly alter, B Lymphocyte Stimulator activity. For example, antibodies or fragments or variants thereof, may be routinely tested for their ability to inhibit B Lymphocyte Stimulator from binding to cells expressing the receptor for B Lymphocyte Stimulator (see Example 3, *infra*).

Selection and Screening for Antibodies that Immunospecifically Bind to Soluble B Lymphocyte Stimulator

Antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be screened in a variety of assays to identify those antibodies that immunospecifically bind to the soluble form of B Lymphocyte Stimulator. In one particular assay, antibodies that bind to the biotinylated soluble form of B Lymphocyte Stimulator in solution are captured on streptavidin coated magnetic beads. This assay may be relatively applied to identify antibodies of the invention that neutralize and/or bind to B Lymphocyte Stimulator. Additionally, antibodies may be assayed in neutralization assays described herein or otherwise known in the art (see Example 3, *infra*). For example, antibodies may be tested for their ability to inhibit soluble B Lymphocyte Stimulator (e.g., biotinylated B Lymphocyte Stimulator) from binding to IM9 cells. In this assay, labeled soluble B Lymphocyte Stimulator (e.g., biotinylated B Lymphocyte Stimulator) is incubated with candidate anti-B Lymphocyte Stimulator antibodies to allow for the formation of B Lymphocyte Stimulator-anti-B Lymphocyte Stimulator antibody complexes. Following incubation, an aliquot of the B Lymphocyte Stimulator-anti-B Lymphocyte Stimulator antibody sample is added to IM9 cells. The binding of soluble B Lymphocyte Stimulator may be determined using techniques known in the art. For example, the binding of biotinylated B Lymphocyte Stimulator to IM9 cells may be detected using a fluorimeter following the addition of streptavidin-delta. Biotinylated B Lymphocyte Stimulator, if it is not bound by antibodies that neutralize B Lymphocyte Stimulator, binds to the cells is detected. Thus, an antibody that decreases the amount of bio-B Lymphocyte Stimulator that binds to IM-9 cells (relative to a control sample in which the B Lymphocyte Stimulator had been preincubated with an irrelevant antibody or no antibody at all)

is identified as one that binds to and neutralizes the soluble form of B Lymphocyte Stimulator. In another assay, antibodies are screened using ELISAs for those antibodies that bind to biotinylated soluble B Lymphocyte Stimulator, but do not bind membrane-bound B Lymphocyte Stimulator, such as, for example, B Lymphocyte Stimulator on membranes from U937 cells (see Examples 2 and 9, *infra*). In these assays, soluble B Lymphocyte Stimulator (e.g., biotinylated B Lymphocyte Stimulator) and membrane-bound B Lymphocyte Stimulator (e.g., on U937 membranes) are incubated in separate samples with the same antibodies and those antibodies that bind to the soluble B Lymphocyte Stimulator (biotinylated B Lymphocyte Stimulator), but not membrane-bound B Lymphocyte Stimulator (e.g., on U937 membranes) are captured and identified.

Antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be tested to identify those antibodies that do not cross-react with APRIL, endoline-alpha, VEGF, TRAIL, TNF-alpha, TNF-beta, Fas-L, LIGHT, and PBS (see Example 4, *infra*). Antibodies may also be tested for their affinity for B Lymphocyte Stimulator using, for example, BIAcore analysis (see Examples 6, 12, 17 and 18 *infra*). Antibodies may also be tested for their ability to stimulate, inhibit, or not alter, B Lymphocyte Stimulator-induced immunoglobulin production and/or B-cell proliferation using techniques known to those of skill in the art. For example, human B-cells, B Lymphocyte Stimulator and antibodies may be incubated together in 96 well plates and ^3H -thymidine incorporation may be measured using a scintillation counter.

Selection and Screening for Antibodies that Immunospecifically Bind to Membrane-Bound B Lymphocyte Stimulator

Antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be screened in a variety of assays to identify those antibodies that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator. In one particular assay, antibodies that bind to B Lymphocyte Stimulator on U937 membranes or immobilized histidine-tagged B Lymphocyte Stimulator are captured. Other cell lines that express B Lymphocyte Stimulator that might be useful for testing antibody binding to membrane-bound form of B Lymphocyte Stimulator include, K-562, HL-60 and THP-1 cells. In another assay, antibodies are screened using ELISAs for those antibodies (or antibody fragments or variants) that bind to B Lymphocyte Stimulator on U937 membranes or to histidine-tagged B Lymphocyte Stimulator. In this assay, antibodies are added to 96 well plates coated with U937 membranes or histidine-tagged B Lymphocyte Stimulator and those antibodies or antibody fragments or variants that bind to the U937 membranes or histidine-tagged B Lymphocyte Stimulator are captured. In another assay, antibodies are screened using ELISAs for those antibodies (or antibody fragments or variants thereof) that do not bind to biotinylated B Lymphocyte Stimulator (soluble B Lymphocyte Stimulator) but bind to membrane-bound B Lymphocyte Stimulator, such as, for example, that on membranes from U937 cells (see Example 2, *infra*). In these assays, soluble B Lymphocyte Stimulator (e.g., biotinylated B Lymphocyte Stimulator) and membrane-bound B Lymphocyte Stimulator (e.g., on U937 membranes) are incubated in separate samples with the same antibodies (or antibody fragments or variants) and those antibodies (or antibody fragments or variants) that do not bind to the soluble B Lymphocyte Stimulator (biotinylated B Lymphocyte Stimulator), but bind the membrane-bound B Lymphocyte Stimulator

(e.g., on U937 membranes) are captured and identified. In other assays, antibodies are screened using ELISAs to determine which of the antibodies (or antibody fragments or variants) that bind to histidine-tagged B Lymphocyte Stimulator or membranes from U937 cells do not cross-react with APRIL, endokine-alpha, VEGI, TRAIL, TNF-alpha, TNF-beta, Fas-L, LIGHT, and PBS (See Example 4, *infra*). ELISAs can also be used to determine which of the antibodies (or antibody fragments or variants) that bind to histidine-tagged B Lymphocyte Stimulator or membranes from U937 cells bind to B Lymphocyte Stimulator in the presence of TNF-alpha (see Example 4, *infra*). Antibodies or fragments or variants thereof that immunospecifically bind to the membrane-bound form of B Lymphocyte Stimulator may also be tested for their affinity for histidine-tagged B Lymphocyte Stimulator using high-throughput BIAcore analysis (see Example 14, *infra*).

Additionally, antibodies of the invention may be screened against cells engineered to express an "uncleavable" form of B Lymphocyte Stimulator in order to determine their specificity for the membrane-bound form of B Lymphocyte Stimulator. Mutations in B Lymphocyte Stimulator which may achieve this result include, but are not limited to, the mutation or deletion of amino acid residues Lys-132 and/or Arg-133 of the B Lymphocyte Stimulator sequence shown in SEQ ID NO:3228. A typical mutagenesis might include mutation of one or both of residues Lys-132 or Arg-133 to alanine residues. Cells expressing such an "uncleavable" form of B Lymphocyte Stimulator provide a profound reagent to use in assaying the ability of antibodies to bind the membrane-bound form of B Lymphocyte Stimulator.

Selection and Screening for Antibodies that Immunospecifically Bind to Soluble and Membrane-Bound B Lymphocyte Stimulator

Antibodies of the invention (including scFvs and other molecules comprising, or alternately consisting of, antibody fragments or variants) may be screened in a variety of assays to identify those antibodies or antibody fragments or variants that immunospecifically bind to the soluble form and membrane-bound form of B Lymphocyte Stimulator. In one particular assay, antibodies that bind to immobilized B Lymphocyte Stimulator are captured. In another assay, antibodies are screened using ELISAs for those antibodies (or antibody fragments or variants) that inhibit the binding of soluble B Lymphocyte Stimulator (e.g. soluble bio-B Lymphocyte Stimulator) to IM-9 cells as described *supra*. In other assays, antibodies are screened using ELISAs for those antibodies that bind to membranes from U937 cells. Additionally, further ELISA assays may be performed using techniques known in the art to determine which antibodies do not cross-react with APRIL, endokine-alpha, VEGI, TRAIL, TNF-alpha, TNF-beta, Fas-L, LIGHT, and PBS, or those antibodies that bind to B Lymphocyte Stimulator in the presence of TNF-alpha (see Example 4 *infra*). Antibodies may be assayed in neutralization assays using techniques described herein or otherwise known in the art. Antibodies that immunospecifically bind to the soluble and membrane-bound forms of B Lymphocyte Stimulator may also be tested for their affinity for B Lymphocyte Stimulator using high-throughput BIAcore analysis.

Antibody Conjugates

The present invention encompasses antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), recombinantly fused or chemically conjugated (including both covalent and non-covalent conjugations) to a heterologous

polypeptide (or portion thereof, preferably at least 10, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90 or at least 100 amino acids of the polypeptide) to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. For example, antibodies of the invention may be used to target heterologous polypeptides to particular cell types (e.g., cells of monocytic lineage and B-cells), either in vitro or in vivo, by fusing or conjugating the heterologous polypeptides to antibodies of the invention that are specific for particular cell surface antigens (e.g., membrane-bound B Lymphocyte Stimulator on cells of monocytic lineage) or which bind antigens that bind particular cell surface receptors (e.g., TACI and/or BCMA located on B cells). Antibodies fused or conjugated to heterologous polypeptides may also be used in in vitro immunoassays and purification methods using methods known in the art. See e.g., Harbor et al., *supra*, and PCT publication WO 93/21232; EP 439,095; Naramura et al., *Immunol. Lett.* 39:91-99 (1994); U.S. Pat. No. 5,474,981; Gillies et al., *PNAS* 89:1428-1432 (1992); Fell et al., *J. Immunol.* 146:2446-2452 (1991), which are incorporated by reference in their entireties.

In one embodiment, a fusion protein comprises a polypeptide having an amino acid sequence of any one of the VH domains referred to in Table 1, and a heterologous polypeptide. In another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VH CDR1s referred to in Table 1, and a heterologous polypeptide. In another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VH CDR2s referred to in Table 1, and a heterologous polypeptide. In a preferred embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VH CDR3s referred to in Table 1 (i.e., SEQ ID NOS:2129-3227), and a heterologous polypeptide.

In another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VL domains referred to in Table 1, and a heterologous polypeptide. In another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VL CDR1s referred to in Table 1, and a heterologous polypeptide. In yet another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VL CDR2s referred to in Table 1, and a heterologous polypeptide. In a preferred embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VL CDR3s referred to in Table 1, and a heterologous polypeptide.

In another embodiment, a fusion protein comprises a polypeptide having the amino acid sequence of any one of the VH domains referred to in Table 1, and one or more VL domains referred to in Table 1, and a heterologous polypeptide. In another embodiment, a fusion protein of the present invention comprises a polypeptide having the amino acid sequence of any one of the VH CDRs referred to in Table 1, and any one of the VL CDRs referred to in Table 1, and a heterologous polypeptide.

The present invention further includes compositions comprising, or alternatively consisting of, heterologous polypeptides fused or conjugated to antibody fragments. For example, the heterologous polypeptides may be fused or conjugated to a Fab fragment, Fd fragment, Fv fragment, F(ab)₂ fragment, or a portion thereof. Methods for fusing or conjugating polypeptides to antibody portions are known in the art. See, e.g., U.S. Pat. Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 9 1/06570; Ashkenazi et al.,

Proc. Natl. Acad. Sci. USA 88: 10535-10539 (1991); Zheng et al., J. Immunol. 154:5590-5600 (1995); and Vil et al., Proc. Natl. Acad. Sci. USA 89:11337-11341 (1992) (said references incorporated by reference in their entireties).

Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to modulate the activities of antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), such methods can be used to generate antibodies with altered activity (e.g., antibodies with higher affinities and lower dissociation rates). See, generally, U.S. Pat. Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al., Curr. Opin. Biotechnol. 8:724-33 (1997); Harayama, Trends Biotechnol. 16(2):76-82 (1998); Hansson, et al., J. Mol. Biol. 287:265-76 (1999); and Lorenzo and Blasco, Biotechniques 24(2):308-13 (1998) (each of these patents and publications are hereby incorporated by reference in its entirety). In one embodiment, polynucleotides encoding antibodies of the invention may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more portions of a polynucleotide encoding an antibody which portions immunospecifically bind to B Lymphocyte Stimulator may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

Moreover, the antibodies of the present invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), can be fused to marker sequences, such as a polypeptides to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine polypeptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, Calif., 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the hemagglutinin "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)) and the "flag" tag (DYKDDDDK, (SEQ ID No: 3238) Stratagene, La Jolla, Calif.).

The present invention further encompasses antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor or prognose the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include, but are not limited to, various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Pat. No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include, but are not limited to,

horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include, but are not limited to, streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include, but are not limited to, umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylantennary fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes, but is not limited to, luminol; examples of bioluminescent materials include, but are not limited to, luciferase, luciferin, and aequorin; and examples of suitable radioactive material include, but are not limited to, iodine (^{131}I , ^{125}I , ^{123}I , ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^3H), indium ($^{115\text{m}}\text{In}$, $^{113\text{m}}\text{In}$, ^{112}In , ^{111}In), and technetium ($^{99\text{m}}\text{Tc}$, $^{99\text{m}}\text{Tc}$), thallium (^{201}Tl), gallium (^{68}Ga , ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm , ^{177}Lu , ^{159}Gd , ^{149}Pm , ^{140}La , ^{175}Yb , ^{166}Ho , ^{90}T , ^{47}Sc , ^{186}Re , ^{188}Re , ^{142}Pr , ^{105}Rh , ^{97}Ru , ^{68}Ge , ^{57}Co , ^{65}Zn , ^{85}Sr , ^{32}P , ^{153}Gd , ^{169}Yb , ^{51}Cr , ^{54}Mn , ^{75}Se , ^{113}Sn , and ^{117}Sn .

Further, an antibody of the invention (including an scFv or other molecule comprising, or alternatively consisting of, antibody fragments or variants thereof), may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytotoxic agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, ^{213}Bi . In specific embodiments, antibodies of the invention are attached to macrocyclic chelators useful for conjugating radiometal ions, including but not limited to, ^{111}In , ^{177}Lu , ^{90}Y , ^{166}Ho , and ^{153}Sm , to polypeptides. In preferred embodiments, the radiometal ion associated with the macrocyclic chelators attached to antibodies of the invention is ^{111}In . In preferred embodiments, the radiometal ion associated with the macrocyclic chelators attached to antibodies of the invention is ^{90}Y . In specific embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane- $\text{N,N',N'',N'''}\text{-tetraacetic acid}$ (DOTA). In other specific embodiments, the DOTA is attached to the antibody of the invention via a linker molecule. Examples of linker molecules useful for conjugating DOTA to a polypeptide are commonly known in the art - see, for example, DeNardo et al., Clin Cancer Res. 4(10):2483-90, 1998; Peterson et al., Bioconjug. Chem. 10(4):553-7, 1999; and Zimmerman et al., Nucl. Med. Biol. 26(8):943-50, 1999 which are hereby incorporated by reference in their entirety.

A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells and includes such molecules as small molecule toxins and enzymatically active toxins of bacterial, fungal, plant, or animal origin, or fragments thereof. Examples include, but are not limited to, paclitaxel, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide (VP-16), teniposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrocortosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, thymidine kinase, endonuclease, RNase, and puromycin and fragments, variants or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cisdichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine), improsulfan, piposulfan, ben-

zodopa, carboquone, meturedopa, uredopa, altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenethiophosphoramidate, trimethylololmelamine, chlornaphazine, cholophosphamide, estramustine, ifosfamide, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, chlorozotocin, fotemustine, nimustine, ranimustine, aclacinomysins, azaserine, cactinomycin, calicheamicin, carabycin, carminomycin, carzophilin, chromomycins, detorubicin, 6-diazo-5-oxo-L-norleucine, epirubicin, esorubicin, idarubicin, marcellomycin, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, quelamycin, rodorubicin, streptonigrin, tubercidin, ubenimex, zinostatin, zorubicin, denopterin, pteropterin, trimetrexate, fludarabine, thiamiprine, ancitabine, azacitidine, 6-azauridine, carmofur, dideoxyuridine, doxifluridine, enocitabine, floxuridine, 5-FU, calsterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone, aminoglutethimide, mitotane, trilostane, frolic acid, aceglutone, aldophosphamide glycoside, aminolevulinic acid, amsacrine, bestabucil, bisantrene, edatraxate, defofamine, dernecolcine, diaziquone, elfomithine, elliptinium acetate, etoglucid, gallium nitrate, hydroxytree, lentinan, lonidamine, mitoguanzone, mopidamol, nitracrine, pentostatin, phenamet, pirarubicin, podophyllinic acid, 2-ethylhydrazide, procarbazine, PSKO, razoxane, sizofiran, spirogermanium, tenuazonic acid, triaziquone, 2,2',2"-trichloronitriethylamine, urethan, vindesine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, gacytosine, arabinoside ("Ara-C"), taxoids, e.g. paclitaxel (TAXOL™, Bristol-Myers Squibb Oncology, Princeton, N.J.) doxetaxel (TAXOTERE™, Rhône-Poulenc Rorer, Antony, France), gemcitabine, ifosfamide, vinorelbine, navelbine, novantrone, teniposide, aminopterin, xeloda, ibandronate, CPT-11, topoisomerase inhibitor RFS 2000, difluoromethylomithine (DMFO), retinoic acid, esperamicins, capecitabine, and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included in this definition are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as antiestrogens including for example tamoxifen, raloxifene, aromatase inhibiting 4(5)imidazoles, 4 hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, torenifene (Fareston), and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin, and pharmaceutically acceptable salts, acids or derivatives of any of the above.

Techniques known in the art may be applied to label antibodies of the invention. Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Pat. Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety) and direct coupling reactions (e.g., Bolton-Hunter and Chloramine-T reaction).

The antibodies of the invention which are conjugates can be used for modifying a given biological response; the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, but are not limited to, for example, a toxin such as abrin, ricin A, alpha toxin, pseudomonas exotoxin, or diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin; a protein such as tumor necrosis factor, alpha-interferon, beta-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF-alpha, TNF-beta, AIM I (see, International Publication No. WO 97/33899), AIM H

(see, International Publication No. WO 97/34911), Fas Ligand (Takahashi et al., *Int. Immunol.*, 6:1567-1574 (1994)), VEGI (see, International Publication No. WO 99/23105), a thrombotic agent or an anti-angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), granulocyte macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), or other growth factors.

Antibodies of the invention (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

Techniques for conjugating a therapeutic moiety to antibodies are well known, see, e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.* 62:119-58 (1982).

Alternatively, an antibody of the invention can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Pat. No. 4,676,980, which is incorporated herein by reference in its entirety.

An antibody of the invention (including an scFv or and other molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

Use of Antibodies for Epitope Mapping

The present invention provides antibodies (including scFvs and other molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that can be used to identify epitopes of B Lymphocyte Stimulator. In particular, the antibodies of the present invention can be used to identify epitopes of human B Lymphocyte Stimulator (SEQ ID NOS: 3228 and/or 3229) or B Lymphocyte Stimulator expressed on human monocytes; murine B Lymphocyte Stimulator (SEQ ID NOS:3230 and/or 3231) or B Lymphocyte Stimulator expressed on murine monocytes; rat B Lymphocyte Stimulator (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form, e.g., on the surface of rat monocytes); or monkey B Lymphocyte Stimulator (e.g., the monkey B Lymphocyte Stimulator polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey B Lymphocyte Stimulator, or B Lymphocyte Stimulator expressed on monkey monocytes using techniques described herein or otherwise known in the art. Fragments which function as epitopes may be produced by any

conventional means. (See, e.g., Houghten, Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985), further described in U.S. Pat. No. 4,631,211.)

Diagnostic Uses of Antibodies

Labeled antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor diseases and/or disorders associated with the aberrant expression and/or activity of B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor. The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample from an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator, and (b) comparing the level of B Lymphocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase or decrease in the assayed level of B Lymphocyte Stimulator compared to the standard level of B Lymphocyte Stimulator is indicative of aberrant expression.

By "biological sample" is intended any fluids and/or cells obtained from an individual, body fluid, body tissue, body cell, cell line, tissue culture, or other source which may contain B Lymphocyte Stimulator protein or mRNA. Body fluids include, but are not limited to, sera, plasma, urine, synovial fluid, spinal fluid, saliva, and mucous. Tissue samples may be taken from virtually any tissue in the body. Tissue samples may also be obtained from autopsy material. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

The invention also provides for the detection of aberrant expression of B Lymphocyte Stimulator receptor comprising (a) assaying the expression of B Lymphocyte Stimulator receptor in a biological sample from an individual using one or more antibodies or fragments or variants thereof that immunospecifically binds only to soluble B Lymphocyte Stimulator, but does not inhibit B Lymphocyte Stimulator/B Lymphocyte Stimulator receptor binding. Such an antibody, by way of an example that is not to be construed as limiting, would be one that is able to capture a biotinylated B Lymphocyte Stimulator from solution (see Example 8), but that would not prevent B Lymphocyte Stimulator from binding to IM-9 cells (see Example 3), and (b) comparing the level of B Lymphocyte Stimulator receptor with a standard level of B Lymphocyte Stimulator receptor, e.g., in normal tissue or cell samples, whereby an increase or decrease in the assayed level of B Lymphocyte Stimulator receptor compared to the standard level of B Lymphocyte Stimulator receptor is indicative of aberrant expression.

Antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor autoimmune disorders and/or immunodeficiencies, and/or diseases or conditions associated therewith. The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample from an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator, and (b) comparing the level of B Lymphocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby

an increase or decrease in the assayed level of B Lymphocyte Stimulator compared to the standard level of B Lymphocyte Stimulator is indicative of an autoimmune disorder or disease and/or an immunodeficiency. In specific embodiments, an increase in the assayed level of B Lymphocyte Stimulator is indicative of an autoimmune disorder or disease. In other specific embodiments, a decrease in the assayed level of B Lymphocyte Stimulator is indicative of an immunodeficiency.

Antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) which specifically bind to B Lymphocyte Stimulator but, do not inhibit B Lymphocyte Stimulator/B Lymphocyte Stimulator receptor binding can be used for diagnostic purposes to detect, diagnose, prognose, or monitor autoimmune disorders and/or immunodeficiencies, and/or diseases or conditions associated therewith. The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator receptor comprising: (a) assaying the expression of B Lymphocyte Stimulator receptor in a biological sample from an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator, and (b) comparing the level of B Lymphocyte Stimulator receptor with a standard level of B Lymphocyte Stimulator receptor, e.g., in normal biological samples, whereby an increase or decrease in the assayed level of B Lymphocyte Stimulator receptor compared to the standard level of B Lymphocyte Stimulator receptor is indicative of an autoimmune disorder or disease and/or an immunodeficiency. In specific embodiments, an increase in the assayed level of B Lymphocyte Stimulator receptor is indicative of an autoimmune disorder or disease. In other specific embodiments, a decrease in the assayed level of B Lymphocyte Stimulator receptor is indicative of an immunodeficiency.

Autoimmune disorders, diseases, or conditions that may be detected, diagnosed, prognosed, or monitored using the antibodies of the invention include, but are not limited to, autoimmune hemolytic anemia, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, autoimmune neutropenia, autoimmune cytopenia, hemolytic anemia, antiphospholipid syndrome, dermatitis, gluten-sensitive enteropathy, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, glomerulonephritis (e.g., IgA nephropathy), Multiple Sclerosis, Neuritis, Uveitis, Ophthalmia, Polyendocrinopathies, Purpura (e.g., Henoch-Schoenlein purpura), Reiter's Disease, Stiff-Man Syndrome, Autoimmune Pulmonary Inflammation, myocarditis, IgA glomerulonephritis, dense deposit disease, rheumatic heart disease, Guillain-Barre Syndrome, diabetes mellitus (e.g. Type I diabetes mellitus or insulin dependent diabetes mellitus), juvenile onset diabetes, and autoimmune inflammatory eye, autoimmune thyroiditis, hypothyroidism (i.e., Hashimoto's thyroiditis, systemic lupus erythematosus, discoid lupus, Goodpasture's syndrome, Pemphigus, Receptor autoimmunities such as, for example, (a) Graves' Disease, (b) Myasthenia Gravis, and (c) insulin resistance, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, rheumatoid arthritis, scleroderma with anti-collagen antibodies, mixed connective tissue disease, polymyositis/dermatomyositis, pernicious anemia (Addison's disease), idiopathic Addison's disease, infertility, glomerulonephritis such as primary glomerulonephritis and IgA nephropathy, bullous pemphigoid, Sjögren's syndrome, diabetes mellitus, and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis), chronic active hepatitis, primary biliary cirrhosis, other endocrine gland failure, vitiligo, vasculitis, post-MI, cardiomy

syndrome, urticaria, atopic dermatitis, asthma, inflammatory myopathies, and other inflammatory, granulomatous, degenerative, and atrophic disorders and other disorders such as inflammatory skin diseases including psoriasis and sclerosis, responses associated with inflammatory bowel disease (such as Crohn's disease and ulcerative colitis), respiratory distress syndrome (including adult respiratory distress syndrome, ARDS), meningitis, encephalitis, colitis, allergic conditions such as eczema and other conditions involving infiltration of T cells and chronic inflammatory responses, arteriosclerosis, leukocyte adhesion deficiency, Reynaud's syndrome, and immune responses associated with acute and delayed hypersensitivity mediated by cytokines and T-lymphocytes typically found in tuberculosis, sarcoidosis, granulomatosis and diseases involving leukocyte diapedesis, central nervous system (CNS) inflammatory disorder, multiple organ injury syndrome, antigen-antibody complex mediated diseases, anti-glomerular basement membrane disease, Lambert-Eaton myasthenic syndrome, Bechet disease, giant cell arthritis, immune complex nephritis, IgA nephropathy, IgM polyneuropathies or autoimmune thrombocytopenia etc.

In specific embodiments, the present invention encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with hypergammaglobulinemia (e.g., AIDS, autoimmune diseases, and some immunodeficiencies). In other specific embodiments, the present invention encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with hypogammaglobulinemia (e.g., an immunodeficiency).

Immunodeficiencies that may be detected, diagnosed, prognosed, or monitored using the antibodies of the invention include, but are not limited to, severe combined immunodeficiency (SCID)X linked, SCID-autosomal, adenosine deaminase deficiency (ADA deficiency), X-linked agammaglobulinemia (XLA), Bruton's disease, congenital agammaglobulinemia, X-linked infantile agammaglobulinemia, acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, transient hypogammaglobulinemia of infancy, unspecified hypogammaglobulinemia, agammaglobulinemia, common variable immunodeficiency (CVID) (acquired), Wiskott-Aldrich Syndrome (WAS), X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, selective IgA deficiency, IgG subclass deficiency (with or without IgA deficiency), antibody deficiency with normal or elevated Igs, immunodeficiency with thymoma, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), selective IgM immunodeficiency, recessive agammaglobulinemia (Swiss type), reticular dysgenesis, neonatal neutropenia, severe congenital leukopenia, thymic aplasia/aplasia or dysplasia with immunodeficiency, ataxia-telangiectasia, short limbed dwarfism, X-linked lymphoproliferative syndrome (XLP), Nezelof syndrome-combined immunodeficiency with Igs, purine nucleoside phosphorylase deficiency (PNP), MHC Class II deficiency (Bare Lymphocyte Syndrome) and severe combined immunodeficiency.

Elevated levels of soluble B Lymphocyte Stimulator have been observed in the serum of patients with Systemic Lupus Erythematosus (SLE). In comparing the sera of 150 SLE patients with that of 38 control individuals, it was found that most of the SLE patients had more than 5 ng/ml of serum B Lymphocyte Stimulator, more than 30% of SLE patients had levels greater than 10 ng/ml, and approximately 10% of SLE patients had serum B Lymphocyte Stimulator levels greater

than 20 ng/ml. In contrast, the majority of normal controls had B Lymphocyte Stimulator levels less than 5 ng/ml, and less than 10% had levels higher than 10 ng/ml. The elevated levels of B Lymphocyte Stimulator protein in sera is present in the soluble form and has biologic activity as assayed by the ability to stimulate anti-IgM treated B cells in vitro. SLE patients with more than 15 ng/ml serum B Lymphocyte Stimulator were also found to have elevated levels of anti-dsDNA antibodies compared to both normal controls and SLE patients with less than 5 ng/ml of serum B Lymphocyte Stimulator.(unpublished data).

In addition the serum of two subgroups of patients which were positive for anti-nuclear antibodies (ANA+) but did not meet the formal requirements of the American College of Rheumatology (ACR) for classification of SLE were analyzed for B Lymphocyte Stimulator levels. The first subgroup of sera was ANA+ sera that came from patients who did not present with the clinical impression of SLE. This group had only slightly elevated levels of B Lymphocyte Stimulator (~9 ng/ml B Lymphocyte Stimulator). The second subgroup however, which was ANA+ sera from patients who presented with the clinical impression of SLE, had significantly increased B Lymphocyte Stimulator levels (~15 ng/ml). These results suggest that an elevated level of B Lymphocyte Stimulator precedes the formal fulfillment of the ACR criteria. The ACR criteria are described in Tan, E. M., et al, *Arthritis and Rheumatism* 25:1271-1277 (1982).

Thus in specific embodiments, antibodies of the invention which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor Systemic Lupus Erythematosus or conditions associated therewith. The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator, and (b) comparing the level of B Lymphocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of B Lymphocyte Stimulator compared to the standard level of B Lymphocyte Stimulator is indicative of SLE.

In other specific embodiments, antibodies of the invention which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor IgA nephropathy or conditions associated therewith. The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator, and (b) comparing the level of B Lymphocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of B Lymphocyte Stimulator compared to the standard level of B Lymphocyte Stimulator is indicative of IgA nephropathy.

In other specific embodiments, antibodies of the invention which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor Sjögren's Syndrome or conditions associated therewith. The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator, and (b) comparing the level of B Lym-

phocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of B Lymphocyte Stimulator compared to the standard level of B Lymphocyte Stimulator is indicative of Sjögren's Syndrome.

In other specific embodiments, antibodies of the invention which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor HIV infection or conditions associated therewith (e.g. AIDS). The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator, and (b) comparing the level of B Lymphocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of B Lymphocyte Stimulator compared to the standard level of B Lymphocyte Stimulator is indicative of HIV infection.

In other specific embodiments, antibodies of the invention which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor Myasthenia Gravis or conditions associated therewith. The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator, and (b) comparing the level of B Lymphocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of B Lymphocyte Stimulator compared to the standard level of B Lymphocyte Stimulator is indicative of Myasthenia Gravis.

In other specific embodiments, antibodies of the invention which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor idiopathic thrombocytopenic purpura (ITP) or conditions associated therewith. The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator and (b) comparing the level of B Lymphocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of B Lymphocyte Stimulator compared to the standard level of B Lymphocyte Stimulator is indicative of idiopathic thrombocytopenic purpura (ITP).

In other specific embodiments, antibodies of the invention which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor hemolytic anemia or conditions associated therewith. The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator; and (b) comparing the level of B Lymphocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of B Lymphocyte Stimulator compared to the standard level of B Lymphocyte Stimulator is indicative of hemolytic anemia.

In other specific embodiments, antibodies of the invention which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor thyroiditis or conditions associated therewith. The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator, and (b) comparing the level of B Lymphocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of B Lymphocyte Stimulator compared to the standard level of B Lymphocyte Stimulator is indicative of thyroiditis.

In other specific embodiments, antibodies of the invention which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor Goodpasture's syndrome or conditions associated therewith. The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator, and (b) comparing the level of B Lymphocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of B Lymphocyte Stimulator compared to the standard level of B Lymphocyte Stimulator is indicative of Goodpasture's syndrome.

In other specific embodiments, antibodies of the invention which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor multiple sclerosis or conditions associated therewith. The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator, and (b) comparing the level of B Lymphocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of B Lymphocyte Stimulator compared to the standard level of B Lymphocyte Stimulator is indicative of multiple sclerosis.

In additional embodiments, antibodies of the invention which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor Rheumatoid Arthritis. The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample (e.g., serum and synovial fluid) of an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator, and (b) comparing the level of B Lymphocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of B Lymphocyte Stimulator compared to the standard level of B Lymphocyte Stimulator is indicative of Rheumatoid arthritis.

In additional embodiments, antibodies of the invention which specifically bind to B Lymphocyte Stimulator can be used for diagnostic purposes to detect, diagnose, prognose, or monitor an immune-based rheumatologic disease, (e.g., SLE, rheumatoid arthritis, CREST syndrome (a variant of scleroderma characterized by calcinosis, Raynaud's phenomenon, esophageal motility disorders, sclerodactyly, and telangiecta-

sia), Seronegative spondyloarthropathy (SpA), Polymyositis/dermatomyositis, Microscopic polyangitis, Hepatitis C-associated arthritis, Takayasu's arthritis, and undifferentiated connective tissue disorder). The invention provides for the detection of aberrant expression of B Lymphocyte Stimulator comprising: (a) assaying the expression of B Lymphocyte Stimulator in a biological sample (e.g., serum and synovial fluid) of an individual using one or more antibodies of the invention that immunospecifically binds to B Lymphocyte Stimulator, and (b) comparing the level of B Lymphocyte Stimulator with a standard level of B Lymphocyte Stimulator, e.g., in normal biological samples, whereby an increase in the assayed level of B Lymphocyte Stimulator compared to the standard level of B Lymphocyte Stimulator is indicative of monitor an immune-based rheumatologic disease.

It has been observed, that serum B Lymphocyte Stimulator levels inversely correlate with nephrotic range proteinuria (>3 gm proteinuria in a 24 hour urine collection) using a sample of 71 SLE patients ($p=0.019$). Proteinuria was determined in 71 SLE patients within one month of phlebotomy for serum B Lymphocyte Stimulator determination. Serum B Lymphocyte Stimulator was classified as low, normal, or high based on the 5th through 95th percentiles for normal controls. Nephrotic-range proteinuria was inversely correlated with serum Neutrokin- α levels. Thus, in specific embodiments, serum levels of B Lymphocyte Stimulator (determined using one or more antibodies of the present invention) in individuals diagnosed with an immune based rheumatologic disease (e.g., SLE, rheumatoid arthritis, CREST syndrome (a variant of scleroderma characterized by calcinosis, Raynaud's phenomenon, esophageal motility disorders, sclerodactyly, and telangiectasia), seronegative spondyloarthropathy (SpA), polymyositis/dermatomyositis, microscopic polyangiitis, hepatitis C-associated arthritis, Takayasu's arthritis, and undifferentiated connective tissue disorder) may be used to determine, diagnose, prognose, or monitor the severity of certain aspects or symptoms of the disease, such as nephrotic-range proteinuria.

In another specific embodiment, antibodies of the invention are used to diagnose, prognose, treat, or prevent conditions associated with CVID, including, but not limited to, conditions associated with acute and recurring infections (e.g., pneumonia, bronchitis, sinusitis, otitis media, sepsis, meningitis, septic arthritis, and osteomyelitis), chronic lung disease, autoimmunity, granulomatous disease, lymphoma, cancers (e.g., cancers of the breast, stomach, colon, mouth, prostate, lung, vagina, ovary, skin, and melanin forming cells (i.e. melanoma), inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis, and ulcerative proctitis), malabsorption, Hodgkin's disease, and Waldenstrom's macroglobulinemia.

The invention provides a diagnostic assay for diagnosing or prognosing a disease or disorder, comprising: (a) assaying for the level of B Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically bind to B Lymphocyte Stimulator, and (b) comparing the level of B Lymphocyte Stimulator with a standard B Lymphocyte Stimulator level, e.g., in a biological sample from a patient without the disease or disorder, whereby an increase or decrease in the assayed B Lymphocyte Stimulator level compared to the standard level of B Lymphocyte Stimulator is indicative of a particular disease or disorder. With respect to cancer, the presence of a relatively high amount of B Lymphocyte Stimulator in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual

clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

In specific embodiments, the presence of a relatively high amount of membrane-bound B Lymphocyte Stimulator in a biological sample is indicative of monocytic cell related leukemias or lymphomas, such as, for example acute myelogenous leukemia and/or the severity thereof.

In other specific embodiments, the presence of a relatively high amount of B Lymphocyte Stimulator receptor in a biological sample (as determined using antibodies of the invention that bind to soluble B Lymphocyte Stimulator, but do not inhibit B Lymphocyte Stimulator/B Lymphocyte Stimulator receptor binding) is indicative of B cell related leukemias or lymphomas (e.g., chronic lymphocytic leukemia, multiple myeloma, non-Hodgkin's lymphoma, and Hodgkin's disease), and/or the severity thereof.

In specific embodiments, the invention provides a diagnostic assay for diagnosing or prognosing Systemic Lupus Erythematosus, comprising: (a) assaying for the level of B Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically bind to B Lymphocyte Stimulator, and (b) comparing the level of B Lymphocyte Stimulator with a standard B Lymphocyte Stimulator level, e.g., in a biological sample from a patient without Systemic Lupus Erythematosus, whereby an increase in the assayed B Lymphocyte Stimulator level compared to the standard level of B Lymphocyte Stimulator is indicative of Systemic Lupus Erythematosus.

In specific embodiments, the invention provides a diagnostic assay for diagnosing or prognosing a Rheumatoid Arthritis, comprising: (a) assaying for the level of B Lymphocyte Stimulator in a biological sample of an individual using one or more antibodies of the invention that immunospecifically bind to B Lymphocyte Stimulator, and (b) comparing the level of B Lymphocyte Stimulator with a standard B Lymphocyte Stimulator level, e.g., in a biological sample from a patient without Rheumatoid Arthritis, whereby an increase or decrease in the assayed B Lymphocyte Stimulator level compared to the standard level of B Lymphocyte Stimulator is indicative of Rheumatoid Arthritis.

The invention provides a diagnostic assay for diagnosing or prognosing a disease or disorder, comprising: (a) assaying for the level of B Lymphocyte Stimulator receptor in cells or a tissue sample of an individual using one or more antibodies of the invention that immunospecifically binds only to soluble B Lymphocyte Stimulator, but does not neutralize B Lymphocyte Stimulator/B Lymphocyte Stimulator receptor binding; and (b) comparing the level of B Lymphocyte Stimulator receptor with a standard B Lymphocyte Stimulator receptor level, e.g., in a tissue sample from a patient without the disease or disorder, whereby an increase or decrease in the assayed B Lymphocyte Stimulator receptor level compared to the standard level of B Lymphocyte Stimulator receptor is indicative of a particular disease or disorder. With respect to cancer, the presence of a relatively high amount of B Lymphocyte Stimulator receptor in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) can be used to assay protein levels in a biological sample using classical immunohistological methods as described herein or as known to those of skill in the art (e.g., see Jalkanen, et al., *J. Cell. Biol.* 101:976-985 (1985); Jalkanen, et al., *J. Cell. Biol.* 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, alkaline phosphatase, and horseradish peroxidase; radioisotopes, such as iodine (^{125}I , ^{123}I , ^{131}I), carbon (^{14}C), sulfur (^{35}S), tritium (^3H), indium (^{111}In , ^{112}In , $^{113\text{m}}\text{In}$, $^{115\text{m}}\text{In}$), technetium ($^{99\text{m}}\text{Tc}$, $^{99\text{m}}\text{Tc}$), thallium (^{201}Tl), gallium (^{68}Ga , ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm , ^{177}Lu , ^{159}Gd , ^{149}Pm , ^{140}La , ^{175}Yb , ^{166}Ho , ^{90}Y , ^{47}Sc , ^{186}Re , ^{188}Re , ^{142}Pr , ^{105}Rh , and ^{97}Ru ; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

One aspect of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled antibody of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically binds to B Lymphocyte Stimulator; b) waiting for a time interval following the administering for permitting the labeled antibody to preferentially concentrate at sites in the subject where B Lymphocyte Stimulator is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled antibody in the subject, such that detection of labeled antibody or fragment thereof above the background level and above or below the level observed in a person without the disease or disorder indicates that the subject has a particular disease or disorder associated with aberrant expression of B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor. Background level can be determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of $^{99\text{m}}\text{Tc}$. The labeled antibody will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S. W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S. W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disorder, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

Presence of the labeled molecule can be detected in the patient using methods known in the art for in vivo scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Pat. No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patient using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

Immunophenotyping

The antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be utilized for immunophenotyping of cell lines and biological samples by their B Lymphocyte Stimulator expression or B Lymphocyte Stimulator receptor expression. Various techniques can be utilized using antibodies, fragments, or variants of the invention to screen for cellular populations (i.e., immune cells, particularly monocytic cells or B-cells) expressing B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor, and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid matrix (i.e., plate), and flow cytometry (see, e.g., U.S. Pat. No. 5,985,660; and Morrison et al., *Cell* 96:737-49 (1999)).

These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e., minimal residual disease (MRD) in acute leukemic patients) and "non-self" cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

In one embodiment, antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) are used to identify cells of monocytic or B cell origin.

Therapeutic Uses of Antibodies

The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention and nucleic acids encoding antibodies (and anti-idiotypic antibodies) of the invention as described herein. The antibodies of the invention can be used to treat, ameliorate or prevent diseases, disorders or conditions associated with the

expression and/or activity of B Lymphocyte Stimulator or B Lymphocyte Stimulator receptor, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant B Lymphocyte Stimulator expression and/or activity or aberrant B Lymphocyte Stimulator receptor expression and/or activity includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

Antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that function as agonists or antagonists of B Lymphocyte Stimulator, preferably of B Lymphocyte Stimulator-induced signal transduction, can be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant B Lymphocyte Stimulator expression, lack of B Lymphocyte Stimulator function, aberrant B Lymphocyte Stimulator receptor expression, or lack of B Lymphocyte Stimulator receptor function. For example, antibodies of the invention which disrupt the interaction between B Lymphocyte Stimulator and its receptor may be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant B Lymphocyte Stimulator expression, excessive B Lymphocyte Stimulator function, aberrant B Lymphocyte Stimulator receptor expression, or excessive of B Lymphocyte Stimulator receptor function. Antibodies of the invention which do not prevent B Lymphocyte Stimulator from binding its receptor but inhibit or downregulate B Lymphocyte Stimulator-induced signal transduction can be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant B Lymphocyte Stimulator expression, excessive B Lymphocyte Stimulator function, aberrant B Lymphocyte Stimulator receptor expression, or excessive B Lymphocyte Stimulator receptor function. In particular, antibodies of the present invention which prevent B Lymphocyte Stimulator-induced signal transduction by specifically recognizing the unbound B Lymphocyte Stimulator, receptor-bound B Lymphocyte Stimulator or both unbound and receptor-bound B Lymphocyte Stimulator can be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant B Lymphocyte Stimulator expression, excessive B Lymphocyte Stimulator function, aberrant B Lymphocyte Stimulator receptor expression, or excessive B Lymphocyte Stimulator receptor function. The ability of an antibody of the invention to inhibit or downregulate B Lymphocyte Stimulator-induced signal transduction may be determined by techniques described herein or otherwise known in the art. For example, B Lymphocyte Stimulator-induced receptor activation and the activation of signaling molecules can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or a signaling molecule by immunoprecipitation followed by western blot analysis (for example, as described herein).

In a specific embodiment, an antibody of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that inhibits or downregulates B Lymphocyte Stimulator activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, at least 50%, at least 45%, at least 40%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to B Lymphocyte Stimulator activity in absence of the antibody is administered to an animal to treat, prevent or ameliorate a disease or dis-

order associated with aberrant B Lymphocyte Stimulator expression, excessive B Lymphocyte Stimulator function, aberrant B Lymphocyte Stimulator receptor expression, or excessive B Lymphocyte Stimulator receptor function. In another embodiment, a combination of antibodies, a combination of antibody fragments, a combination of antibody variants, or a combination of antibodies, antibody fragments, and/or variants that inhibit or downregulate B Lymphocyte Stimulator activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, at least 50%, at least 45%, at least 40%, at least 35%, at least 30%, at least 25%, at least 20%, or at least 10% relative to B Lymphocyte Stimulator activity in absence of said antibodies, antibody fragments, and/or antibody variants are administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant B Lymphocyte Stimulator expression, excessive B Lymphocyte Stimulator function, aberrant B Lymphocyte Stimulator receptor expression, or excessive B Lymphocyte Stimulator receptor function.

Further, antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) which activate B Lymphocyte Stimulator-induced signal function can be administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant B Lymphocyte Stimulator expression, lack of B Lymphocyte Stimulator function, aberrant B Lymphocyte Stimulator receptor expression, or lack of B Lymphocyte Stimulator receptor function. These antibodies may potentiate or activate either all or a subset of the biological activities of B Lymphocyte Stimulator-mediated receptor activation, for example, by inducing multimerization of B Lymphocyte Stimulator and/or multimerization of the receptor. The antibodies of the invention may be administered with or without being pre-complexed with B Lymphocyte Stimulator. In a specific embodiment, an antibody of the present invention that increases B Lymphocyte Stimulator activity by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% relative to B Lymphocyte Stimulator activity in absence of the antibody is administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant B Lymphocyte Stimulator expression, lack of B Lymphocyte Stimulator function, aberrant B Lymphocyte Stimulator receptor expression, or lack of B Lymphocyte Stimulator receptor function. In another embodiment, a combination of antibodies, a combination of antibody fragments, a combination of antibody variants, or a combination of antibodies, antibody fragments and/or antibody variants that increase B Lymphocyte Stimulator activity by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% relative to B Lymphocyte Stimulator activity in absence of the said antibodies or antibody fragments and/or antibody variants is administered to an animal to treat, prevent or ameliorate a disease or disorder associated with aberrant B Lymphocyte Stimulator expression or lack of B Lymphocyte Stimulator function or aberrant B Lymphocyte Stimulator receptor expression or lack of B Lymphocyte Stimulator receptor function.

One or more antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically

bind to B Lymphocyte Stimulator may be used locally or systemically in the body as a therapeutic. The antibodies of this invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may also be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

The antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy, anti-tumor agents, anti-angiogenesis and anti-inflammatory agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments, or variants, (e.g., derivatives), or nucleic acids, are administered to a human patient for therapy or prophylaxis.

It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to B Lymphocyte Stimulator, or polynucleotides encoding antibodies that immunospecifically bind to B Lymphocyte Stimulator, for both immunoassays directed to and therapy of disorders related to B Lymphocyte Stimulator polynucleotides or polypeptides, including fragments thereof. Such antibodies will preferably have an affinity for B Lymphocyte Stimulator and/or B Lymphocyte Stimulator fragments. Preferred binding affinities include those with a dissociation constant or K_D less than or equal to 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, or 10^{-5} M. More preferably, antibodies of the invention bind B Lymphocyte Stimulator polypeptides or fragments or variants thereof with a dissociation constant or K_D less than or equal to 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, or 10^{-8} M. Even more preferably, antibodies of the invention bind B Lymphocyte Stimulator polypeptides or fragments or variants thereof with a dissociation constant or K_D less than or equal to 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, or 10^{-15} M. The invention encompasses antibodies that bind B Lymphocyte Stimulator polypeptides with a dissociation constant or K_D that is within any one of the ranges that are between each of the individual recited values.

In a preferred embodiment, antibodies of the invention neutralize B Lymphocyte Stimulator activity. In another preferred embodiment, antibodies of the invention inhibit B cell proliferation.

In a preferred embodiment, antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) inhibit or reduce binding of the soluble form of B Lymphocyte Stimulator to a B Lymphocyte Stimulator receptor. In another preferred embodiment antibodies of the invention inhibit or reduce B cell proliferation induced by the soluble form of B Lymphocyte Stimulator. In another preferred embodiment antibodies of the invention inhibit or reduce immunoglobulin production induced by the soluble form of B Lymphocyte Stimulator.

In a preferred embodiment, antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) inhibit or reduce binding of membrane-bound B Lymphocyte Stimulator to a B Lymphocyte Stimulator receptor. In another preferred

embodiment, antibodies of the invention inhibit or reduce B cell proliferation induced by the membrane-bound form of B Lymphocyte Stimulator. In another preferred embodiment, antibodies of the invention inhibit or reduce immunoglobulin production induced by the membrane bound form of B Lymphocyte Stimulator.

In a preferred embodiment, antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) inhibit or reduce binding of both the soluble and membrane-bound forms of B Lymphocyte Stimulator to a B Lymphocyte Stimulator receptor. In another preferred embodiment, antibodies of the invention inhibit or reduce B cell proliferation induced by either or both forms of B Lymphocyte Stimulator. In another preferred embodiment, antibodies of the invention inhibit or reduce immunoglobulin production induced by either or both forms of B Lymphocyte Stimulator.

In one embodiment, the invention provides a method of delivering antibody conjugates of the invention to targeted cells, such as, for example, monocytic cells expressing the membrane-bound form of B Lymphocyte Stimulator, or B cells expressing a B Lymphocyte Stimulator receptor.

In one embodiment, the invention provides a method for the specific delivery of antibodies and antibody conjugates of the invention to cells by administering molecules of the invention that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering antibodies or antibody conjugates of the invention (e.g., antibodies conjugated with radioisotopes, toxins, or cytotoxic prodrugs). In a specific embodiment, the invention provides a method for the specific destruction of cells of monocytic lineage (e.g., monocytic cell related leukemias or lymphomas, such as, for example acute myelogenous leukemia) by administering antibodies or antibody conjugates of the invention (e.g., antibodies conjugated with radioisotopes, toxins, or cytotoxic prodrugs) that immunospecifically bind the membrane-bound form of B Lymphocyte Stimulator. In another specific embodiment, the invention provides a method for the specific destruction of cells of B cell lineage (e.g., B cell related leukemias or lymphomas (e.g., chronic lymphocytic leukemia, multiple myeloma, non-Hodgkin's lymphoma, and Hodgkin's disease) by administering antibodies or antibody conjugates of the invention (e.g., antibodies conjugated with radioisotopes, toxins, or cytotoxic prodrugs) that bind soluble B Lymphocyte Stimulator, but do not inhibit B Lymphocyte Stimulator binding to a B Lymphocyte Stimulator receptor on B cells.

In another preferred embodiment antibodies of the invention (including antibody fragments and variants) promote or enhance B cell proliferation induced by the soluble form of B Lymphocyte Stimulator. In another preferred embodiment, antibodies of the invention (including antibody fragments and variants) promote or enhance B cell proliferation induced by the membrane or soluble form of APRIL. In another preferred embodiment antibodies of the invention (including antibody fragments and variants) increase or enhance immunoglobulin production induced by the soluble form of B Lymphocyte Stimulator. In another preferred embodiment antibodies of the invention (including antibody fragments and variants)

increase or enhance immunoglobulin production induced by the membrane bound or soluble form of APRIL. In another preferred embodiment antibodies of the invention (including antibody fragments and variants) increase or enhance immunoglobulin production in response to T cell dependent immunogens. In another preferred embodiment antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance immunoglobulin production in response to T cell independent immunogens.

In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate immune disorders. Immune disorders include, but are not limited to, autoimmune disorders (e.g., arthritis, graft rejection, Hashimoto's thyroiditis, insulin-dependent diabetes, lupus, idiopathic thrombocytopenic purpura, systemic lupus erythematosus and multiple sclerosis), elective IgA deficiency, ataxia-telangiectasia, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, severe combined immunodeficiency (SCID), Wiskott-Aldrich syndrome, idiopathic hyper-edsinophilic syndrome, monocytic leukemoid reaction, monocytic leukocytosis, monocytic leukopenia, monocytopenia, monocytosis, and graft or transplant rejection.

As discussed herein, antibodies and antibody compositions of the invention, may be used to treat, prevent, ameliorate, diagnose or prognose various immune system-related disorders and/or conditions associated with these disorders, in mammals, preferably humans. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of antibody and antibody compositions of the invention that can inhibit an immune response, particularly the proliferation of B cells and/or the production of immunoglobulins, may be an effective therapy in treating and/or preventing autoimmune disorders. Thus, in preferred embodiments, antibodies and antibody compositions of the invention are used to treat, prevent, ameliorate, diagnose and/or prognose an autoimmune disorder, or condition(s) associated with such disorder.

Autoimmune disorders and conditions associated with these disorders that may be treated, prevented, ameliorated, diagnosed and/or prognosed with the therapeutic and pharmaceutical compositions of the invention include, but are not limited to, autoimmune hemolytic anemia, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, autoimmune neutropenia, autoimmunocytopenia, hemolytic anemia, antiphospholipid syndrome, dermatitis, gluten-sensitive enteropathy, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, glomerulonephritis (e.g., IgA nephropathy), Multiple Sclerosis, Neuritis, Uveitis Ophthalmia, Polyendocrinopathies, Purpura (e.g., Henloch-Schoenlein purpura), Reiter's Disease, Stiff-Man Syndrome, Autoimmune Pulmonary Inflammation, myocarditis, IgA glomerulonephritis, dense deposit disease, rheumatic heart disease, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disease.

Additional autoimmune disorders and conditions associated with these disorders that may be treated, prevented, ameliorated, diagnosed and/or prognosed with the therapeutic and pharmaceutical compositions of the invention include, but are not limited to, autoimmune thyroiditis, hypothyroidism (i.e., Hashimoto's thyroiditis) (often characterized, e.g., by cell-mediated and humoral thyroid cytotoxicity), systemic lupus erythematosus (often characterized, e.g., by circulating and locally generated immune complexes), discoid lupus,

Goodpasture's syndrome (often characterized, e.g., by anti-basement membrane antibodies), Pemphigus (often characterized, e.g., by epidermal acantholytic antibodies), Receptor autoimmunities such as, for example, (a) Graves' Disease (often characterized, e.g., by TSH receptor antibodies), (b) Myasthenia Gravis (often characterized, e.g., by acetylcholine receptor antibodies), and (c) insulin resistance (often characterized, e.g., by insulin receptor antibodies), autoimmune hemolytic anemia (often characterized, e.g., by phagocytosis of antibody-sensitized RBCs), autoimmune thrombocytopenic purpura (often characterized, e.g., by phagocytosis of antibody-sensitized platelets).

Additional autoimmune disorders and conditions associated with these disorders that may be treated, prevented, ameliorated, diagnosed and/or prognosed with the therapeutic and pharmaceutical compositions of the invention include, but are not limited to, rheumatoid arthritis (often characterized, e.g., by immune complexes in joints), scleroderma with anti-collagen antibodies (often characterized, e.g., by nucleolar and other nuclear antibodies), mixed connective tissue disease (often characterized, e.g., by antibodies to extractable nuclear antigens (e.g., ribonucleoprotein)), polymyositis/dermatomyositis (often characterized, e.g., by non-histone ANA), pernicious anemia (often characterized, e.g., by antiparietal cell, microsomes, and intrinsic factor antibodies), idiopathic Addison's disease (often characterized, e.g., by humoral and cell-mediated adrenal cytotoxicity, infertility (often characterized, e.g., by antispermatozoal antibodies), glomerulonephritis (often characterized, e.g., by glomerular basement membrane antibodies or immune complexes) such as primary glomerulonephritis and IgA nephropathy, bullous pemphigoid (often characterized, e.g., by IgG and complement in basement membrane), Sjögren's syndrome (often characterized, e.g., by multiple tissue antibodies, and/or a specific nonhistone ANA (SS-B)), diabetes mellitus (often characterized, e.g., by cell-mediated and humoral islet cell antibodies), and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis) (often characterized, e.g., by beta-adrenergic receptor antibodies), chronic active hepatitis (often characterized, e.g., by smooth muscle antibodies), primary biliary cirrhosis (often characterized, e.g., by mitochondrial antibodies), other endocrine gland failure (often characterized, e.g., by specific tissue antibodies in some cases), vitiligo (often characterized, e.g., by melanocyte antibodies), vasculitis (often characterized, e.g., by Ig and complement in vessel walls and/or low serum complement), post-MI (often characterized, e.g., by myocardial antibodies), cardiomyopathy (often characterized, e.g., by myocardial antibodies), urticaria (often characterized, e.g., by IgG and IgM antibodies to IgE), atopic dermatitis (often characterized, e.g., by IgG and IgM antibodies to IgE), asthma (often characterized, e.g., by IgG and IgM antibodies to IgE), inflammatory myopathies, and many other inflammatory, granulomatous, degenerative, and atrophic disorders.

In a preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, a member of the group: autoimmune hemolytic anemia, as primary glomerulonephritis, IgA glomerulonephritis, Goodpasture's syndrome, idiopathic thrombocytopenia, Multiple Sclerosis, Myasthenia Gravis, Pemphigus, polymyositis/dermatomyositis, relapsing polychondritis, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, Uveitis, vasculitis, and primary biliary cirrhosis.

In another preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, pre-

vent, ameliorate, diagnose or prognosis, an immune based-rheumatologic disease, such as, for example, SLE, rheumatoid arthritis, CREST syndrome (a variant of scleroderma characterized by calcinosis, Raynaud's phenomenon, esophageal motility disorders, sclerodactyly, and telangiectasia.), Seronegative spondyloarthropathy (SpA), polymyositis/dermatomyositis, microscopic polyangiitis, hepatitis C-associated arthritis, Takayasu's arthritis, and undifferentiated connective tissue disorder.

In a specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognosis, rheumatoid arthritis and/or medical conditions associated therewith.

For example, an antibody, or antibodies, of the present invention are used to treat patients with clinical diagnosis of rheumatoid arthritis (RA). The patient treated preferably will not have a B cell malignancy. Moreover, the patient is optionally further treated with any one or more agents employed for treating RA such as salicylate; nonsteroidal anti-inflammatory drugs such as indomethacin, phenylbutazone, phenylacetic acid derivatives (e.g. ibuprofen and fenoprofen), naphthalene acetic acids (naproxen), pyrroleallanoic acid (tometin), indoleacetic acids (sulindac), halogenated anthranilic acid (meclofenamate sodium), piroxicam, zomepirac and diflunisal; antimalarials such as chloroquine; gold salts; penicillamine; or immunosuppressive agents such as methotrexate or corticosteroids in dosages known for such drugs or reduced dosages. Preferably however, the patient is only treated with an antibody, or antibodies, of the present invention. Antibodies of the present invention are administered to the RA patient according to a dosing schedule as described infra, which may be readily determined by one of ordinary skill in the art. The primary response is determined by the Paulus index (Paulus et al. *Arthritis Rheum.* 33:477-484 (1990)), i.e. improvement in morning stiffness, number of painful and inflamed joints, erythrocyte sedimentation (ESR), and at least a 2-point improvement on a 5-point scale of disease severity assessed by patient and by physician. Administration of an antibody, or antibodies, of the present invention will alleviate one or more of the symptoms of RA in the patient treated as described above.

In a specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognosis, lupus and/or medical conditions associated therewith. Lupus-associated conditions that may be treated, prevented, ameliorated, prognosed and/or diagnosed with the antibodies and antibody compositions of the invention include, but are not limited to, hematologic disorders (e.g., hemolytic anemia; leukopenia, lymphopenia, and thrombocytopenia), immunologic disorders (e.g., anti-DNA antibodies, and anti-Sm antibodies), rashes, photosensitivity, oral ulcers, arthritis, fever, fatigue, weight loss, serositis (e.g., pleuritis (pleurisy)), renal disorders (e.g., nephritis), neurological disorders (e.g., seizures, peripheral neuropathy, CNS related disorders), gastrointestinal disorders, Raynaud phenomenon, and pericarditis. In a preferred embodiment, therapeutic and pharmaceutical compositions of the invention are used to treat, prevent, ameliorate, diagnose, or prognosis, renal disorders associated with systemic lupus erythematosus. In a most preferred embodiment therapeutic and pharmaceutical compositions of the invention are used to treat, prevent, ameliorate, diagnose, or prognosis, nephritis associated with systemic lupus erythematosus. In another most preferred embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate lupus or glomerular nephritis.

In a further specific embodiment, antibodies of the invention are used to treat, inhibit, prognoses diagnose or prevent hemolytic anemia. For example, patients diagnosed with autoimmune hemolytic anemia (AIHA), e.g. cryoglobulinemia or Coombs positive anemia, are treated with an antibody, or antibodies, of the present invention. AIHA is an acquired hemolytic anemia due to auto-antibodies that react with the patient's red blood cells. The patient treated preferably will not have a B cell malignancy. Further adjunct therapies (such as glucocorticoids, prednisone, azathioprine, cyclophosphamide, vinca-laden platelets or Danazol) may be combined with the antibody therapy, but preferably the patient is treated with an antibody, or antibodies, of the present invention as a single-agent throughout the course of therapy. Antibodies of the present invention are administered to the hemolytic anemia patient according to a dosing schedule as described infra, which may be readily determined by one of ordinary skill in the art. Overall response rate is determined based upon an improvement in blood counts, decreased requirement for transfusions, improved hemoglobin levels and/or a decrease in the evidence of hemolysis as determined by standard chemical parameters. Administration of an antibody, or antibodies of the present invention will improve any one or more of the symptoms of hemolytic anemia in the patient treated as described above. For example, the patient treated as described above will show an increase in hemoglobin and an improvement in chemical parameters of hemolysis or return to normal as measured by serum lactic dehydrogenase and/or bilirubin.

In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognosis, Sjögren's Syndrome and/or medical conditions associated therewith.

In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognosis, HIV infection and/or medical conditions associated therewith (e.g. AIDS).

In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognosis, Myasthenia gravis and/or medical conditions associated therewith.

In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognosis, IgA nephropathy and/or medical conditions associated therewith.

In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognoses hemolytic anemia and/or medical conditions associated therewith.

In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognosis, thyroiditis and/or medical conditions associated therewith.

In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognosis, Goodpasture's Syndrome and/or medical conditions associated therewith.

In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognosis, multiple sclerosis and/or medical conditions associated therewith.

In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognosis, chronic lymphocytic leukemia (CLL) and/or medical conditions associated therewith.

In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, multiple myeloma and/or medical conditions associated therewith.

In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose Non-Hodgkin's lymphoma and/or medical conditions associated therewith.

In another specific preferred embodiment, therapeutic and pharmaceutical compositions of the invention, are used to treat, prevent, ameliorate, diagnose or prognose, Hodgkin's disease and/or medical conditions associated therewith.

In another specific embodiment, antibodies of the invention are used to treat, inhibit, prognose, diagnose or prevent adult immune thrombocytopenic purpura. Adult immune thrombocytopenic purpura (ITP) is a relatively rare hematologic disorder that constitutes the most common of the immune-mediated cytopenias. The disease typically presents with severe thrombocytopenia that may be associated with acute hemorrhage in the presence of normal to increased megakaryocytes in the bone marrow. Most patients with ITP have an IgG antibody directed against target antigens on the outer surface of the platelet membrane, resulting in platelet sequestration in the spleen and accelerated reticuloendothelial destruction of platelets (Bussell, J. B. *Hematol. Oncol. Clin. North Am.* (4):179 (1990)). A number of therapeutic interventions have been shown to be effective in the treatment of ITP. Steroids are generally considered first-line therapy, after which most patients are candidates for intravenous immunoglobulin (IVIG), splenectomy, or other medical therapies including vincristine or immunosuppressive/cytotoxic agents. Up to 80% of patients with ITP initially respond to a course of steroids, but far fewer have complete and lasting remissions. Splenectomy has been recommended as standard second-line therapy for steroid failures, and leads to prolonged remission in nearly 60% of cases yet may result in reduced immunity to infection. Splenectomy is a major surgical procedure that may be associated with substantial morbidity (15%) and mortality (2%). MG has also been used as second line medical therapy, although only a small proportion of adult patients with ITP achieve remission. Therapeutic options that would interfere with the production of autoantibodies by activated B cells without the associated morbidities that occur with corticosteroids and/or splenectomy would provide an important treatment approach for a proportion of patients with ITP. Patients with clinical diagnosis of ITP are treated with an antibody, or antibodies of the present invention, optionally in combination with steroid therapy. The patient treated will not have a B cell malignancy. Antibodies of the present invention are administered to the RA patient according to a dosing schedule as described infra, which may be readily determined by one of ordinary skill in the art. Overall patient response rate is determined based upon a platelet count determined on two consecutive occasions two weeks apart following treatments as described above. See, George et al. "Idiopathic Thrombocytopenic Purpura: A Practice Guideline Developed by Explicit Methods for The American Society of Hematology", *Blood* 88:340 (1996), expressly incorporated herein by reference.

In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate an IgE-mediated allergic reaction or histamine-mediated allergic reaction. Examples of allergic reactions include, but are not limited to, asthma, rhinitis, eczema, chronic urticaria, and atopic dermatitis. In another embodiment, therapeutic or pharmaceutical compo-

sitions of the invention are administered to an animal to treat, prevent, or ameliorate anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility. In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate or modulate inflammation or an inflammatory disorder. Examples of chronic and acute inflammatory disorders that may be treated prevented or ameliorated with the therapeutic and pharmaceutical compositions of the invention include, but are not limited to, chronic prostatitis, granulomatous prostatitis and malacoplasia, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, Crohn's disease, inflammatory bowel disease, chronic and acute inflammatory pulmonary diseases, bacterial infection, psoriasis, septicemia, cerebral malaria, arthritis, gastroenteritis, and glomerular nephritis.

In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate ischemia and arteriosclerosis. Examples of such disorders include, but are not limited to, reperfusion damage (e.g., in the heart and/or brain) and cardiac hypertrophy.

Therapeutic or pharmaceutical compositions of the invention, may also be administered to modulate blood clotting and to treat or prevent blood clotting disorders, such as, for example, antibody-mediated thrombosis (i.e., antiphospholipid antibody syndrome (APS)). For example, therapeutic or pharmaceutical compositions of the invention, may inhibit the proliferation and differentiation of cells involved in producing anticardiolipin antibodies. These compositions of the invention can be used to treat, prevent, ameliorate, diagnose, and/or prognose thrombotic related events including, but not limited to, stroke (and recurrent stroke), heart attack, deep vein thrombosis, pulmonary embolism, myocardial infarction, coronary artery disease (e.g., antibody-mediated coronary artery disease), thrombosis, graft reocclusion following cardiovascular surgery (e.g., coronary arterial bypass grafts, recurrent fetal loss, and recurrent cardiovascular thromboembolic events).

Therapeutic or pharmaceutical compositions of the invention, may also be administered to treat, prevent, or ameliorate organ rejection or graft-versus-host disease (GVHD) and/or conditions associated therewith. Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of antibodies of the invention, that inhibit an immune response, may be an effective therapy in preventing organ rejection or GVHD.

In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate a disease or disorder diseases associated with increased apoptosis including, but not limited to, AIDS, neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration), myelodysplastic syndromes (such as aplastic anemia), ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia. In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat,

prevent or ameliorate bone marrow failure, for example, aplastic anemia and myelodysplastic syndrome.

In another embodiment, therapeutic or pharmaceutical compositions of the invention are administered to an animal to treat, prevent or ameliorate growth, progression, and/or metastases of malignancies and proliferative disorders associated with increased cell survival, or the inhibition of apoptosis. Examples of such disorders, include, but are not limited to, leukemia (e.g., acute leukemia such as acute lymphocytic leukemia and acute myelocytic leukemia), neoplasms, tumors (e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, and retinoblastoma), heavy chain disease, metastases, or any disease or disorder characterized by uncontrolled cell growth.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used to treat or prevent a disorder characterized by hypergammaglobulinemia (e.g., AIDS, autoimmune diseases, and some immunodeficiencies).

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used to treat or prevent a disorder characterized by deficient serum immunoglobulin production, recurrent infections, and/or immune system dysfunction. Moreover, therapeutic or pharmaceutical compositions of the invention may be used to treat or prevent infections of the joints, bones, skin, and/or parotid glands, blood-borne infections (e.g., sepsis, meningitis, septic arthritis, and/or osteomyelitis), autoimmune diseases (e.g., those disclosed herein), inflammatory disorders, and malignancies, and/or any disease or disorder or condition associated with these infections, diseases, disorders and/or malignancies) including, but not limited to, CVID, other primary immune deficiencies, HIV disease, CLL, recurrent bronchitis, sinusitis, otitis media, conjunctivitis, pneumonia, hepatitis, meningitis, herpes zoster (e.g., severe herpes zoster), and/or pneumocystis carinii.

Therapeutic or pharmaceutical compositions of the invention of the invention thereof, may be used to diagnose, prognose, treat or prevent one or more of the following diseases or disorders, or conditions associated therewith: primary immunodeficiencies, immune-mediated thrombocytopenia, Kawasaki syndrome, bone marrow transplant (e.g., recent bone marrow transplant in adults or children), chronic B-cell lymphocytic leukemia, HIV infection (e.g., adult or pediatric HIV infection), chronic inflammatory demyelinating polyneuropathy, and post-transfusion purpura.

Additionally, therapeutic or pharmaceutical compositions of the invention may be used to diagnose, prognose, treat or prevent one or more of the following diseases, disorders, or conditions associated therewith, Guillain-Barre syndrome, anemia (e.g., anemia associated with parvovirus B19,

patients with stable multiple myeloma who are at high risk for infection (e.g., recurrent infection), autoimmune hemolytic anemia (e.g., warm-type autoimmune hemolytic anemia), thrombocytopenia (e.g., neonatal thrombocytopenia), and immune-mediated neutropenia), transplantation (e.g., cytomegalovirus (CMV)-negative recipients of CMV-positive organs), hypogammaglobulinemia (e.g., hypogammaglobulinemic neonates with risk factor for infection or morbidity), epilepsy (e.g., intractable epilepsy), systemic vasculitic syndromes, myasthenia gravis (e.g., decompensation in myasthenia gravis), dermatomyositis, and polymyositis.

Additional preferred embodiments of the invention include, but are not limited to, the use of therapeutic or pharmaceutical compositions of the invention in the following applications:

Administration to an animal (e.g., mouse, rat, rabbit, hamster, guinea pig, pigs, micro-pig, chicken, camel, goat, horse, cow, sheep, dog, cat, non-human primate, and human, most preferably human) to boost the immune system to produce increased quantities of one or more antibodies (e.g., IgG, IgA, IgM, and IgE), to induce higher affinity antibody production (e.g., IgG, IgA, IgM, and IgE), and/or to increase an immune response. In a specific nonexclusive embodiment, therapeutic or pharmaceutical compositions of the invention are administered to boost the immune system to produce increased quantities of IgG. In another specific nonexclusive embodiment, antibodies of the are administered to boost the immune system to produce increased quantities of IgA. In another specific nonexclusive embodiment antibodies of the invention are administered to boost the immune system to produce increased quantities of IgM.

Administration to an animal (including, but not limited to, those listed above, and also including transgenic animals) incapable of producing functional endogenous antibody molecules or having an otherwise compromised endogenous immune system, but which is capable of producing human immunoglobulin molecules by means of a reconstituted or partially reconstituted immune system from another animal (see, e.g., published PCT Application Nos. WO98/24893, WO/9634096, WO/9633735, and WO/9110741).

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a vaccine adjuvant that enhances immune responsiveness to specific antigen. In a specific embodiment, the vaccine is an antibody described herein. In another specific embodiment, the vaccine adjuvant is a polynucleotide described herein (e.g., an antibody polynucleotide genetic vaccine adjuvant). As discussed herein, therapeutic or pharmaceutical compositions of the invention may be administered using techniques known in the art, including but not limited to, liposomal delivery, recombinant vector delivery, injection of naked DNA, and gene gun delivery.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an adjuvant to enhance tumor-specific immune responses.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an adjuvant to enhance anti-viral immune responses. Anti-viral immune responses that may be enhanced using the compositions of the invention as an adjuvant, include, but are not limited to, virus and virus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: AIDS, meningitis, Dengue, EBV, and hepatitis (e.g., hepatitis B). In another

specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: HIV/AIDS, Respiratory syncytial virus, Dengue, Rotavirus, Japanese B encephalitis, Influenza A and B, Parainfluenza, Measles, Cytomegalovirus, Rabies, Junin, Chikungunya, Rift Valley fever, Herpes simplex, and yellow fever. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to the HIV gp120 antigen.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an adjuvant to enhance anti-bacterial or anti-fungal immune responses. Anti-bacterial or anti-fungal immune responses that may be enhanced using the compositions of the invention as an adjuvant, include bacteria or fungus and bacteria or fungus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: tetanus, Diphtheria, botulism, and meningitis type B. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: *Vibrio cholerae*, *Mycobacterium leprae*, *Salmonella typhi*, *Salmonella paratyphi*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, Group B streptococcus, *Shigella* spp., Enterotoxigenic *Escherichia coli*, Enterohemorrhagic *E. coli*, *Borrelia burgdorferi*, and *Plasmodium* (malaria).

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an adjuvant to enhance anti-parasitic immune responses. Anti-parasitic immune responses that may be enhanced using the compositions of the invention as an adjuvant, include parasite and parasite associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a parasite. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to *Plasmodium* (malaria).

In a specific embodiment, compositions of the invention may be administered to patients as vaccine adjuvants. In a further specific embodiment, compositions of the invention may be administered as vaccine adjuvants to patients suffering from an immune-deficiency. In a further specific embodiment, compositions of the invention may be administered as vaccine adjuvants to patients suffering from HIV.

In a specific embodiment, compositions of the invention may be used to increase or enhance antigen-specific antibody responses to standard and experimental vaccines. In a specific embodiment, compositions of the invention may be used to enhance seroconversion in patients treated with standard and experimental vaccines. In another specific embodiment, compositions of the invention may be used to increase the repertoire of antibodies recognizing unique epitopes in response to standard and experimental vaccination.

In a preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance antigen-specific antibody responses to standard and experimental vaccines by regulating binding of the soluble form of B Lymphocyte Stimulator to a B Lymphocyte Stimulator receptor (e.g., BCMA and TACI). In another preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance

antigen-specific antibody responses to standard and experimental vaccines by regulating binding of the soluble form of APRIL to an APRIL receptor (e.g., BCMA and TACI).

In a preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance seroconversion in patients treated with standard and experimental vaccines by regulating binding of the soluble form of B Lymphocyte Stimulator to B Lymphocyte Stimulator receptor (e.g., BCMA and TACI). In another preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance seroconversion in patients treated with standard and experimental vaccines by regulating binding of the soluble form of APRIL to an APRIL receptor (e.g., BCMA and TACI).

In a preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance the repertoire of antibodies recognizing unique epitopes in response to standard and experimental vaccination by regulating binding of the soluble form of B Lymphocyte Stimulator to a B Lymphocyte Stimulator receptor (e.g., BCMA and TACI). In another preferred embodiment, antibodies of the invention (including antibody fragments and variants, and anti-antibody antibodies) increase or enhance the repertoire of antibodies recognizing unique epitopes in response to standard and experimental vaccination by regulating binding of the soluble form of APRIL to an APRIL receptor (e.g., BCMA and TACI).

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a stimulator of B cell responsiveness to pathogens.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent that elevates the immune status of an individual prior to their receipt of immunosuppressive therapies.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to induce higher affinity antibodies.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to increase serum immunoglobulin concentrations.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to accelerate recovery of immunocompromised individuals.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to boost immunoresponsiveness among aged populations.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an immune system enhancer prior to, during, or after bone marrow transplant and/or other transplants (e.g., allogeneic or xenogeneic organ transplantation). With respect to transplantation, compositions of the invention may be administered prior to, concomitant with, and/or after transplantation. In a specific embodiment, compositions of the invention are administered after transplantation, prior to the beginning of recovery of T-cell populations. In another specific embodiment, compositions of the invention are first administered after transplantation after the beginning of recovery of T cell populations, but prior to full recovery of B cell populations.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to boost immunoresponsiveness among B cell immunodeficient individuals, such as, for example, an individual who has undergone a partial or complete splenectomy. B cell immunodeficiencies that may be ameliorated or treated by administering the antibodies and/or compositions of the invention include,

but are not limited to, severe combined immunodeficiency (SCID)-X linked, SCID autosomal, adenosine deaminase deficiency (ADA deficiency), X-linked agammaglobulinemia (XLA), Bruton's disease, congenital agammaglobulinemia, X-linked infantile agammaglobulinemia, acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, transient hypogammaglobulinemia of infancy, unspecified hypogammaglobulinemia, agammaglobulinemia, common variable immunodeficiency (CVID) (acquired), Wiskott-Aldrich Syndrome (WAS), X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, selective IgA deficiency, IgG subclass deficiency (with or without IgA deficiency), antibody deficiency with normal or elevated Igs, immunodeficiency with thymoma, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), selective IgM immunodeficiency, recessive agammaglobulinemia (Swiss type), reticular dysgenesis, neonatal neutropenia, severe congenital leukopenia, thymic aplasia/aplasia or dysplasia with immunodeficiency, ataxia-telangiectasia, short limbed dwarfism, X-linked lymphoproliferative syndrome (XLP), Nezelof syndrome-combined immunodeficiency with Igs, purine nucleoside phosphorylase deficiency (PNP), MHC Class II deficiency (Bare Lymphocyte Syndrome) and severe combined immunodeficiency.

In a specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate selective IgA deficiency.

In another specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate ataxia-telangiectasia.

In another specific embodiment antibodies and/or compositions of the invention are administered to treat or ameliorate common variable immunodeficiency.

In another specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate X-linked agammaglobulinemia.

In another specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate severe combined immunodeficiency (SCID).

In another specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate Wiskott-Aldrich syndrome.

In another specific embodiment, antibodies and/or compositions of the invention are administered to treat or ameliorate X-linked Ig deficiency with hyper IgM.

As an agent to boost immunoresponsiveness among individuals having an acquired loss of B cell function. Conditions resulting in an acquired loss of B cell function that may be ameliorated or treated by administering antibodies and/or compositions of the invention include, but are not limited to, HIV Infection, AIDS, bone marrow transplant, and B cell chronic lymphocytic leukemia (CLL).

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to boost immunoresponsiveness among individuals having a temporary immune deficiency. Conditions resulting in a temporary immune deficiency that may be ameliorated or treated by administering antibodies and/or compositions of the invention include, but are not limited to, recovery from viral infections (e.g., influenza), conditions associated with malnutrition, recovery from infectious mononucleosis, or conditions associated with stress, recovery from measles, recovery from blood transfusion, recovery from surgery.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a regulator of antigen presentation by monocytes, dendritic cells, T cells and/or B-cells. In one embodiment, antibody polypeptides or polynucleotides enhance antigen presentation or antagonize antigen presentation in vitro or in vivo. Moreover, in related embodiments, this enhancement or antagonization of antigen presentation may be useful in anti-tumor treatment or to modulate the immune system.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a mediator of mucosal immune responses. The expression of B Lymphocyte Stimulator on monocytes, the expression of B Lymphocyte Stimulator receptor on B cells, and the responsiveness of B cells to B Lymphocyte Stimulator suggests that it may be involved in exchange of signals between B cells and monocytes or their differentiated progeny. This activity is in many ways analogous to the CD40-CD154 signalling between B cells and T cells. Anti-B Lymphocyte Stimulator antibodies and compositions of the invention may therefore be good regulators of T cell independent immune responses to environmental pathogens. In particular, the unconventional B cell populations (CD5+) that are associated with mucosal sites and responsible for much of the innate immunity in humans may respond to antibodies or compositions of the invention thereby enhancing or inhibiting individual's immune status.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an agent to direct an individual's immune system towards development of a humoral response (i.e. TH2) as opposed to a TH1 cellular response.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a means to induce tumor proliferation and thus make it more susceptible to anti-neoplastic agents. For example, multiple myeloma is a slowly dividing disease and is thus refractory to virtually all anti-neoplastic regimens. If these cells were forced to proliferate more rapidly, their susceptibility profile would likely change.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a monocyte cell specific binding protein to which specific activators or inhibitors of cell growth may be attached. The result would be to focus the activity of such activators or inhibitors onto normal, diseased, or neoplastic B cell populations.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a B cell specific binding protein to which specific activators or inhibitors of cell growth may be attached. The result would be to focus the activity of such activators or inhibitors onto normal, diseased, or neoplastic B cell populations.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a means of detecting monocytic cells by virtue of its specificity. This application may require labeling the protein with biotin or other agents (e.g., as described herein) to afford a means of detection.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a means of detecting B-lineage cells by virtue of its specificity. This application may require labeling the protein with biotin or other agents (e.g., as described herein) to afford a means of detection.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a stimulator of B cell production in pathologies such as AIDS, chronic lymphocyte disorder and/or Common Variable immunodeficiency.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as part of a monocyte selection device the function of which is to isolate monocytes from a heterogeneous mixture of cell types. Antibodies of the invention could be coupled to a solid support to which monocytes would then specifically bind. Unbound cells would be washed out and the bound cells subsequently eluted. A non-limiting use of this selection would be to allow purging of tumor cells from, for example, bone marrow or peripheral blood prior to transplant.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as part of a B cell selection device the function of which is to isolate B cells from a heterogeneous mixture of cell types. Antibodies of the invention (that do not inhibit B Lymphocyte Stimulator/B Lymphocyte Stimulator Receptor interaction) binding soluble B Lymphocyte Stimulator could be coupled to a solid support to which B cells would then specifically bind. Unbound cells would be washed out and the bound cells subsequently eluted. A non-limiting use of this selection would be to allow purging of tumor cells from, for example, bone marrow or peripheral blood prior to transplant.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a therapy for generation and/or regeneration of lymphoid tissues following surgery, trauma or genetic defect.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a gene-based therapy for genetically inherited disorders resulting in immuno-incompetence such as observed among SCID patients.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as an antigen for the generation of antibodies to inhibit or enhance B Lymphocyte Stimulator mediated responses.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a means of activating monocytes/macrophages to defend against parasitic diseases that effect monocytes such as *Leishmania*.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as pretreatment of bone marrow samples prior to transplant. Such treatment would increase B cell representation and thus accelerate recovery.

In a specific embodiment, therapeutic or pharmaceutical compositions of the invention are used as a means of regulating secreted cytokines that are elicited by B Lymphocyte Stimulator and/or B Lymphocyte Stimulator receptor.

Antibody polypeptides or polynucleotides of the invention may be used to modulate IgE concentrations in vitro or in vivo.

Additionally, antibody polypeptides or polynucleotides of the invention may be used to treat, prevent, and/or diagnose IgE-mediated allergic reactions. Such allergic reactions include, but are not limited to, asthma, rhinitis, and eczema.

In a specific embodiment, antibody polypeptides or polynucleotides of the invention, are administered to treat, prevent, diagnose, and/or ameliorate selective IgA deficiency.

In another specific embodiment antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate ataxia-telangiectasia.

In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate common variable immunodeficiency.

In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate X-linked agammaglobulinemia.

In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate severe combined immunodeficiency (SCID).

In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate Wiskott-Aldrich syndrome.

In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate X-linked Ig deficiency with hyper IgM. In a specific embodiment antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate X-linked Ig deficiency with hyper IgM.

In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, and/or diagnose chronic myelogenous leukemia, acute myelogenous leukemia, leukemia, histiocytic leukemia, monocytic leukemia (e.g., acute monocytic leukemia), leukemic reticulosis, Shilling Type monocytic leukemia, and/or other leukemias derived from monocytes and/or monocytic cells and/or tissues.

In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate monocytic leukemoid reaction, as seen, for example, with tuberculosis.

In another specific embodiment, antibody polypeptides or polynucleotides of the invention are administered to treat, prevent, diagnose, and/or ameliorate monocytic leukocytosis, monocytic leukopenia, monocytopenia, and/or monocytosis.

In a specific embodiment, antibody polypeptides or polynucleotides of the invention are used to treat, prevent, detect, and/or diagnose monocyte disorders and/or diseases, and/or conditions associated therewith.

In a specific embodiment, antibody polypeptides or polynucleotides of the invention are used to treat, prevent, detect, and/or diagnose primary B lymphocyte disorders and/or diseases, and/or conditions associated therewith. In one embodiment, such primary B lymphocyte disorders, diseases, and/or conditions are characterized by a complete or partial loss of humoral immunity. Primary B lymphocyte disorders, diseases, and/or conditions associated therewith that are characterized by a complete or partial loss of humoral immunity and that may be prevented, treated, detected and/or diagnosed with compositions of the invention include, but are not limited to, X-Linked Agammaglobulinemia (XLA), severe combined immunodeficiency disease (SCID), and selective IgA deficiency.

In a preferred embodiment antibody polypeptides or polynucleotides of the invention are used to treat, prevent, and/or diagnose diseases or disorders affecting or conditions associated with any one or more of the various mucous membranes of the body. Such diseases or disorders include, but are not limited to, for example, mucositis, mucoclasia, mucocolitis, mucocutaneous leishmaniasis (such as, for example, American leishmaniasis, leishmaniasis americana, nasopharyngeal leishmaniasis, and New World leishmaniasis), mucocutaneous lymph node syndrome (for example, Kawasaki disease), mucoenteritis, mucoepidermoid carcinoma, mucoepidermoid tumor, mucoepithelial dysplasia, mucoid adenocarcinoma, mucoid degeneration, myxoid degeneration; myxomatous degeneration; myxomatosis, mucoid

medial degeneration (for example, cystic medial necrosis), mucopolipidosis (including, for example, mucopolipidosis I, mucopolipidosis II, mucopolipidosis III, and mucopolipidosis IV), mucolysis disorders, mucomembranous enteritis, mucoen-
 5 teritis, mucopolysaccharidosis (such as, for example, type I mucopolysaccharidosis (i.e., Hurler's syndrome), type II mucopolysaccharidosis (i.e., Scheie's syndrome or type V
 10 mucopolysaccharidosis), type II mucopolysaccharidosis (i.e., Hunter's syndrome), type III mucopolysaccharidosis (i.e., Sanfilippo's syndrome), type IV mucopolysaccharido-
 15 sis (i.e., Morquio's syndrome), type VI mucopolysaccharido-
 sis (i.e., Maroteaux-Lamy syndrome), type VII mucopolysac-
 charidosis (i.e., mucopolysaccharidosis due to beta-
 glucuronidase deficiency), and mucosulfatidosis),
 mucopolysacchariduria, mucopurulent conjunctivitis, muco-
 20 pus, mucomycosis (i.e., zygomycosis), mucosal disease
 (i.e., bovine virus diarrhea), mucous colitis (such as, for
 example, mucocolitis and myxomembranous colitis), and
 mucoviscidosis (such as, for example, cystic fibrosis, cystic
 25 fibrosis of the pancreas, Clarke-Hadfield syndrome, fibrocys-
 tic disease of the pancreas, mucoviscidosis, and viscidosis).
 In a highly preferred embodiment, antibody polypeptides or
 polynucleotides of the invention are used to treat, prevent,
 and/or diagnose mucositis, especially as associated with che-
 motherapy.

In a preferred embodiment, antibody polypeptides or poly-
 nucleotides of the invention are used to treat, prevent, and/or
 30 diagnose diseases or disorders affecting or conditions asso-
 ciated with sinusitis.

An additional condition, disease or symptom that can be
 treated, prevented, and/or diagnosed by antibody polypep-
 35 tides or polynucleotides of the invention is osteomyelitis.

An additional condition, disease or symptom that can be
 treated, prevented, and/or diagnosed by antibody polypep-
 40 tides or polynucleotides of the invention is endocarditis.

All of the above described applications as they may apply
 to veterinary medicine.

Antibody polypeptides or polynucleotides of the invention
 may be used to treat, prevent, and/or diagnose diseases and
 disorders of the pulmonary system (e.g., bronchi such as, for
 example, sinopulmonary and bronchial infections and condi-
 45 tions associated with such diseases and disorders and other
 respiratory diseases and disorders. In specific embodiments,
 such diseases and disorders include, but are not limited to,
 bronchial adenoma, bronchial asthma, pneumonia (such as,
 e.g., bronchial pneumonia, bronchopneumonia, and tubercu-
 50 lous bronchopneumonia), chronic obstructive pulmonary dis-
 ease (COPD), bronchial polyps, bronchiectasia (such as, e.g.,
 bronchiectasia sicca, cylindrical bronchiectasis, and saccular
 bronchiectasis), bronchiolar adenocarcinoma, bronchiolar
 carcinoma, bronchiolitis (such as, e.g., exudative bronchioli-
 55 tis, bronchiolitis fibrosa obliterans, and proliferative bronchi-
 olitis), bronchiolo-alveolar carcinoma, bronchitic asthma,
 bronchitis (such as, e.g., asthmatic bronchitis, Castellani's
 bronchitis, chronic bronchitis, croupous bronchitis, fibrinous
 bronchitis, hemorrhagic bronchitis, infectious avian bronchi-
 60 tis, obliterative bronchitis, plastic bronchitis, pseudomem-
 branous bronchitis, putrid bronchitis, and verminous bronchi-
 tis), bronchocentric granulomatosis, bronchoedema,
 bronchoesophageal fistula, bronchogenic carcinoma, bron-
 chogenic cyst, broncholithiasis, bronchomalacia, broncho-
 mycosis (such as, e.g., bronchopulmonary aspergillosis),
 bronchopulmonary spirochetosis, hemorrhagic bronchitis,
 bronchoplethra, bronchospasm, bronchostaxis, bronchostenosis,
 Biot's respiration, bronchial respiration, Kussmaul respi-
 65 ration, Kussmaul-Kien respiration, respiratory acidosis, res-
 piratory alkalosis, respiratory distress syndrome of the

newborn, respiratory insufficiency, respiratory scleroma, res-
 piratory syncytial virus, and the like.

In a specific embodiment, antibody polypeptides or poly-
 nucleotides of the invention are used to treat, prevent, and/or
 5 diagnose chronic obstructive pulmonary disease (COPD).

In another embodiment, antibody polypeptides or poly-
 nucleotides of the invention are used to treat, prevent, and/or
 10 diagnose fibroses and conditions associated with fibroses,
 including, but not limited to, cystic fibrosis (including such
 fibroses as cystic fibrosis of the pancreas, Clarke-Hadfield
 syndrome, fibrocystic disease of the pancreas, mucoviscido-
 15 sis, and viscidosis), endomyocardial fibrosis, idiopathic ret-
 roperitoneal fibrosis, leptomenigeal fibrosis, mediastrial
 fibrosis, nodular subepidermal fibrosis, pericentral fibrosis,
 perimuscular fibrosis, pipestem fibrosis, replacement fibro-
 20 sis, subadventitial fibrosis, and Symmers' clay pipestem
 fibrosis.

In another embodiment, therapeutic or pharmaceutical
 compositions of the invention are administered to an animal
 to beat, prevent or ameliorate infectious diseases. Infectious
 diseases include diseases associated with yeast, fungal, viral
 and bacterial infections. Viruses causing viral infections
 which can be treated or prevented in accordance with this
 invention include, but are not limited to, retroviruses (e.g.,
 25 human T-cell lymphotropic virus (HTLV) types I and II and
 human immunodeficiency virus (HIV)), herpes viruses (e.g.,
 herpes simplex virus (HSV) types I and II, Epstein-Barr virus,
 HHV6-HHV8, and cytomegalovirus), adenoviruses (e.g.,
 lassa fever virus), paramyxoviruses (e.g., morbillivirus virus,
 30 human respiratory syncytial virus, mumps, and pneumovi-
 rus), adenoviruses, bunyaviruses (e.g., hantavirus), cornavi-
 ruses, filoviruses (e.g., Ebola virus), flaviviruses (e.g., hepa-
 titis C virus (HCV), yellow fever virus, and Japanese
 encephalitis virus), hepadnaviruses (e.g., hepatitis B viruses
 35 (HBV)), orthomyoviruses (e.g., influenza viruses A, B and
 C), papovaviruses (e.g., papillomaviruses), picomaviruses
 (e.g., rhinoviruses, enteroviruses and hepatitis A viruses),
 poxviruses, reoviruses (e.g., rotaviruses), togaviruses (e.g.,
 rubella virus), rhabdoviruses (e.g., rabies virus). Microbial
 40 pathogens causing bacterial infections include, but are not
 limited to, *Streptococcus pyogenes*, *Streptococcus pneumo-
 niae*, *Neisseria gonorrhoea*, *Neisseria meningitidis*, *Coryne-
 bacterium diphtheriae*, *Clostridium botulinum*, *Clostridium
 45 peفرingens*, *Clostridium tetani*, *Haemophilus influenzae*,
Klebsiella pneumoniae, *Klebsiella ozaenae*, *Klebsiella rhi-
 noscleromatis*, *Staphylococcus aureus*, *Vibrio cholerae*,
Escherichia coli, *Pseudomonas aeruginosa*, *Campylobacter
 (Vibrio) fetus*, *Campylobacter jejuni*, *Aeromonas hydrophila*,
Bacillus cereus, *Edwardsiella tarda*, *Yersinia enterocolitica*,
Yersinia pestis, *Yersinia pseudotuberculosis*, *Shigella dysen-
 50 teriae*, *Shigella flexneri*, *Shigella sonnei*, *Salmonella typhimurium*,
Treponema pallidum, *Treponema pertenue*, *Treponema
 carateneum*, *Borrelia vincentii*, *Borrelia burgdorferi*, *Lep-
 tospira icterohemorrhagiae*, *Mycobacterium tuberculosis*,
Toxoplasma gondii, *Pneumocystis carinii*, *Francisella tula-
 55 rensis*, *Brucella abortus*, *Brucella suis*, *Brucella melitensis*,
Mycoplasma spp., *Rickettsia prowazeki*, *Rickettsia* *tsutsugamushi*,
Chlamydia spp., and *Helicobacter pylori*.

Gene Therapy

In a specific embodiment, nucleic acids comprising
 sequences encoding antibodies or functional derivatives
 thereof, are administered to treat, inhibit or prevent a disease
 or disorder associated with aberrant expression and/or activ-
 65 ity of B Lymphocyte Stimulator and/or its receptor, by way of
 gene therapy. Gene therapy refers to therapy performed by the
 administration to a subject of an expressed or expressible

nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect

Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

For general reviews of the methods of gene therapy, see Goldspiel et al., *Clinical Pharmacy* 12:488-505 (1993); Wu and Wu, *Biotherapy* 3:87-95 (1991); Tolstoshev, *Ann. Rev. Pharmacol. Toxicol.* 32:573-596 (1993); Mulligan, *Science* 260:926-932 (1993); and Morgan and Anderson, *Ann. Rev. Biochem.* 62:191-217 (1993); May, *TIBTECH* 1 (5):155-215 (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), *Current Protocols in Molecular Biology*, John Wiley & Sons, NY (1993); and Kriegler, *Gene Transfer and Expression, A Laboratory Manual*, Stockton Press, NY (1990).

In a preferred aspect, a composition of the invention comprises, or alternatively consists of, nucleic acids encoding an antibody, said nucleic acids being part of an expression vector that expresses the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acids have promoters, preferably heterologous promoters, operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, *Proc. Natl. Acad. Sci. USA* 86:8932-8935 (1989); Zijlstra et al., *Nature* 342:435438 (1989). In specific embodiments, the expressed antibody molecule is an scFv; alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments or variants thereof, of an antibody.

Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid-carrying vectors, or indirect, in which case, cells are first transformed with the nucleic acids in vitro, then transplanted into the patient. These two approaches are known, respectively, as in vivo or ex vivo gene therapy.

In a specific embodiment, the nucleic acid sequences are directly administered in vivo, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, e.g., by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, e.g., by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Pat. No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, e.g., Wu and Wu, *J. Biol. Chem.* 262:4429-4432 (1987)) (which can be used to target cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted in vivo for cell specific uptake

and expression, by targeting a specific receptor (see, e.g., PCT Publications WO 92/06 180; WO 92/22635; W092/203 16; W093/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, *Proc. Natl. Acad. Sci. USA* 86:8932-8935 (1989); Zijlstra et al., *Nature* 342:435438 (1989)).

In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention or fragments or variants thereof are used. For example, a retroviral vector can be used (see Miller et al., *Meth. Enzymol.* 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., *Biotherapy* 6:29 1-302 (1994), which describes the use of a retroviral vector to deliver the *mdr 1* gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., *J. Clin. Invest.* 93:644-651 (1994); Klein et al., *Blood* 83:1467-1473 (1994); Salmons and Gunzberg, *Human Gene Therapy* 4:129-141 (1993); and Grossman and Wilson, *Curr. Opin. in Genetics and Devel.* 3:110-114 (1993).

Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, *Current Opinion in Genetics and Development* 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout et al., *Human Gene Therapy* 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., *Science* 252:434 (1991); Rosenfeld et al., *Cell* 68:143-155 (1992); Mastangeli et al., *J. Clin. Invest.* 91:225-234 (1993); PCT Publication W094/12649; and Wang, et al., *Gene Therapy* 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al, *Proc. Soc. Exp. Biol. Med.* 204:289-300 (1993); U.S. Pat. No. 5,436,146).

Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

In this embodiment, the nucleic acid is introduced into a cell prior to administration in vivo of the resulting recombinant cell. Such introduction can be carried out by any method known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-gene mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, *Meth. Enzymol.*

217:599-618 (1993); Cohen et al., *Meth. Enzymol.* 217:618-44 (1993); *Clin Pharma. Ther.* 29:69-92m (1985)) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as T lymphocytes, B lymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody or fragment thereof are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered in vivo for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained in vitro can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT Publication WO 94/08598; Stemple and Anderson, *Cell* 71:973-985 (1992); Rheinwald, *Meth. Cell Bio.* 21A:229 (1980); and Pittelkow and Scott, *Mayo Clinic Proc.* 61:771 (1986)).

In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by controlling the presence or absence of the appropriate inducer of transcription.

Demonstration of Therapeutic or Prophylactic Utility of a Composition

The compounds of the invention are preferably tested in vitro, and then in vivo for the desired therapeutic or prophylactic activity, prior to use in humans. For example, in vitro assays which can be used to determine whether administration of a specific antibody or composition of the present invention is indicated, include in vitro cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered an antibody or composition of the present invention, and the effect of such an antibody or composition of the present invention upon the tissue sample is observed. In various specific embodiments, in vitro assays can be carried out with representative cells of cell types involved in a patient's disorder, to determine if an antibody or composition of the present invention has a desired effect upon such cell types. Preferably, the antibodies or compositions of the invention are also tested in in vitro assays and animal model systems prior to administration to humans.

Antibodies or compositions of the present invention for use in therapy can be tested for their toxicity in suitable animal

model systems, including but not limited to rats, mice, chicken, cows, monkeys, and rabbits. For in vivo testing of an antibody or composition's toxicity any animal model system known in the art may be used.

Efficacy in treating or preventing viral infection may be demonstrated by detecting the ability of an antibody or composition of the invention to inhibit the replication of the virus, to inhibit transmission or prevent the virus from establishing itself in its host, or to prevent, ameliorate or alleviate the symptoms of disease a progression. The treatment is considered therapeutic if there is, for example, a reduction in viral load, amelioration of one or more symptoms, or a decrease in mortality and/or morbidity following administration of an antibody or composition of the invention.

Antibodies or compositions of the invention can be tested for the ability to induce the expression of cytokines such as IFN- γ , by contacting cells, preferably human cells, with an antibody or composition of the invention or a control antibody or control composition and determining the ability of the antibody or composition of the invention to induce one or more cytokines. Techniques known to those of skill in the art can be used to measure the level of expression of cytokines. For example, the level of expression of cytokines can be measured by analyzing the level of RNA of cytokines by, for example, RT-PCR and Northern blot analysis, and by analyzing the level of cytokines by, for example, immunoprecipitation followed by western blot analysis and ELISA. In a preferred embodiment, a compound of the invention is tested for its ability to induce the expression of IFN- γ .

Antibodies or compositions of the invention can be tested for their ability to modulate the biological activity of immune cells by contacting immune cells, preferably human immune cells (e.g. T-cells, B-cells, and Natural Killer cells), with an antibody or composition of the invention or a control compound and determining the ability of the antibody or composition of the invention to modulate (i.e., increase or decrease) the biological activity of immune cells. The ability of an antibody or composition of the invention to modulate the biological activity of immune cells can be assessed by detecting the expression of antigens, detecting the proliferation of immune cells (i.e., B-cell proliferation), detecting the activation of signaling molecules, detecting the effector function of immune cells, or detecting the differentiation of immune cells. Techniques known to those of skill in the art can be used for measuring these activities. For example, cellular proliferation can be assayed by ^3H -thymidine incorporation assays and trypan blue cell counts. Antigen expression can be assayed, for example, by immunoassays including, but not limited to, competitive and non-competitive assay systems using techniques such as western blots, immunohistochemistry radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays and FACS analysis. The activation of signaling molecules can be assayed, for example, by kinase assays and electrophoretic shift assays (EMSAs). In a preferred embodiment, the ability of an antibody or composition of the invention to induce B-cell proliferation is measured. In another preferred embodiment, the ability of an antibody or composition of the invention to modulate immunoglobulin expression is measured.

Antibodies or compositions of the invention can be tested for their ability to reduce tumor formation in in vitro, ex vivo and in vivo assays. Antibodies or compositions of the inven-

tion can also be tested for their ability to inhibit viral replication or reduce viral load in in vitro and in vivo assays. Antibodies or compositions of the invention can also be tested for their ability to reduce bacterial numbers in in vitro and in vivo assays known to those of skill in the art. Antibodies or compositions of the invention can also be tested for their ability to alleviate one or more symptoms associated with cancer, an immune disorder (e.g., an inflammatory disease), a neurological disorder or an infectious disease. Antibodies or compositions of the invention can also be tested for their ability to decrease the time course of the infectious disease. Further, antibodies or compositions of the invention can be tested for their ability to increase the survival period of animals suffering from disease or disorder, including cancer, an immune disorder or an infectious disease. Techniques known to those of skill in the art can be used to analyze the function of the antibodies or compositions of the invention in vivo.

Therapeutic/Prophylactic Compositions and Administration

The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of antibody (or fragment or variant thereof) or pharmaceutical composition of the invention, preferably an antibody of the invention. In a preferred aspect, an antibody or fragment or variant thereof is substantially purified (i.e., substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to, animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably a human.

Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

Various delivery systems are known and can be used to administer antibody or fragment or variant thereof of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the antibody or antibody fragment, receptor-mediated endocytosis (see, e.g., Wu and Wu, *J. Biol. Chem.* 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

In a specific embodiment, it may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material,

including membranes, such as sialattic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

In another embodiment, the composition can be delivered in a vesicle, in particular a liposome (see Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); Lopez-Berestein, *ibid.*, pp. 3 17-327; see generally *ibid.*).

In yet another embodiment, the composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, *CRC Crit. Rev. Biomed. Eng.* 14:20 1 (1987); Buchwald et al., *Surgery* 88:507 (1980); Saudek et al., *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used (see *Medical Applications of Controlled Release*, Langer and Wise (eds.), CRC Press, Boca Raton, Fla. (1974); *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Bal (eds.), Wiley, New York (1984); Ranger and Peppas, *J. Macromol. Sci. Rev. Macromol. Chem.* 23:61 (1983); see also Levy et al., *Science* 228: 190 (1985); During et al., *Ann. Neurol.* 25:35 1 (1989); Howard et al., *J. Neurosurg.* 7 1:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in *Medical Applications of Controlled Release*, *supra*, vol. 2, pp. 115-138 (1984)).

Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

In a specific embodiment where the composition of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered in vivo to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Pat. No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biologic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (see e.g., Joliot et al., *Proc. Natl. Acad. Sci. USA* 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of an antibody or a fragment thereof, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried

skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin. Such compositions will contain a therapeutically effective amount of the antibody or fragment thereof, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

The compositions of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The amount of the composition of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgement of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of admin-

istration of therapeutic or pharmaceutical compositions of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by modifications such as, for example, lipidation.

The antibodies and antibody compositions of the invention may be administered alone or in combination with other adjuvants. Adjuvants that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, alum, alum plus deoxycholate (ImmunogAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG, and MPL. In a specific embodiment, antibody and antibody compositions of the invention are administered in combination with alum. In another specific embodiment, antibody and antibody compositions of the invention are administered in combination with QS-21. Further adjuvants that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, Monophosphoryl lipid immunomodulator, AdjuVax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella), polio, varicella, tetanus/diphtheria, hepatitis A, hepatitis B, haemophilus influenzae B, whooping cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis, and/or PNEUMOVAX-23™. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

In another specific embodiment, antibody and antibody compositions of the invention are used in combination with PNEUMOVAX-23™ to treat, prevent, and/or diagnose infection and/or any disease, disorder, and/or condition associated therewith. In one embodiment, antibody and antibody compositions of the invention are used in combination with PNEUMOVAX-23™ to treat, prevent, and/or diagnose any Gram positive bacterial infection and/or any disease, disorder, and/or condition associated therewith. In another embodiment, antibody and antibody compositions of the invention are used in combination with PNEUMOVAX-23™ to treat, prevent, and/or diagnose infection and/or any disease, disorder, and/or condition associated with one or more members of the genus *Enterococcus* and/or the genus *Streptococcus*. In another embodiment, antibody and antibody compositions of the invention are used in any combination with PNEUMOVAX-23™ to treat, prevent, and/or diagnose infection and/or any disease, disorder, and/or condition associated with one or more members of the Group B streptococci. In another embodiment, antibody and antibody compositions of the invention are used in combination with PNEUMOVAX-23™ to treat, prevent, and/or diagnose infection and/or any disease, disorder, and/or condition associated with *Streptococcus pneumoniae*.

The antibody and antibody compositions of the invention may be administered alone or in combination with other therapeutic agents, including but not limited to, chemotherapeutic agents, antibiotics, antivirals, steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic

agents and cytokines. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

In one embodiment, the antibody and antibody compositions of the invention are administered in combination with other members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPG, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), TRAIL, AIM-II (International Publication No. WO 97/34911), APRIL (J. Exp. Med. 188(6): 1185-1190 (1998)), endoline-alpha (International Publication No. WO 98/07880), Neutrokin-alpha (International Application Publication No. WO 98/18921), OPG, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-1BB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TR6 (International Publication No. WO 98/30694), TR7 (International Publication No. WO 98/41629), TRANK, TR9 (International Publication No. WO 98/56892), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with CD40 ligand (CD40L), a soluble form of CD40L (e.g., AVRENDTM), biologically active fragments, variants, or derivatives of CD40L, anti-CD40L antibodies (e.g., agonistic or antagonistic antibodies), and/or anti-CD40 antibodies (e.g., agonistic or antagonistic antibodies).

In an additional embodiment, the antibody and antibody compositions of the invention are administered alone or in combination with an anti-angiogenic agent(s). Anti-angiogenic agents that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, Angiostatin (Entremed, Rockville, Md.), Tropin-1 (Boston Life Sciences, Boston, Mass.), anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel (Taxol), Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, VEGF, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium

orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include, but are not limited to, platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, 1991); Sulphated Polysaccharide Peptidoglycan Complex (SP-PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha, alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, 1992); Chymostatin (Tomkinson et al., Biochem J. 286:475480, 1992); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, 1990); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, 1987); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, 1987); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4-chloroanthranilic acid disodium or "CCA"; (Takeuchi et al., Agents Actions 36:312-316, 1992); and metalloproteinase inhibitors such as BB94.

Additional anti-angiogenic factors that may also be utilized within the context of the present invention include Thalidomide, (Celgene, Warren, N.J.); Angiostatic steroid; AGM-1470 (H. Brem and J. Folkman J. Pediatr. Surg. 28:445-51 (1993)); an integrin alpha v beta 3 antagonist (C. Storgard et al., J. Clin. Invest. 103:47-54 (1999)); carboxyaminoimidazole; Carboxyamidotriazole (CAI) (National Cancer Institute, Bethesda, Md.); Conbreastatin A-4 (CA4P) (OXIGENE, Boston, Mass.); Squalamine (Maganin Pharmaceuticals, Plymouth Meeting, Pa.); TNP-470, (Tap Pharmaceuticals, Deerfield, Ill.); ZD-0101 AstraZeneca (London, UK); APRA (CT2584); Benefin, Byrostatin-1 (SC339555); CGP-41251 (PKC 412); CM101; Dexrazoxane (ICRF187); DMXAA; Endostatin; Flavopridiol; Genestein; GTE; ImmTher, Iressa (ZD1839); Octreotide (Somatostatin); Pauretin; Penicillamine; Photopoint; PI-88; Prinomastat (AG-3340) Purytin; Suradista (FCE26644); Tamoxifen (Nolvadex); Tazarotene; Tetrathiomolybdate; Xeloda (Capecitabine); and 5-Fluorouracil.

Anti-angiogenic agents that may be administered in combination with the compounds of the invention may work

through a variety of mechanisms including, but not limited to, inhibiting proteolysis of the extracellular matrix, blocking the function of endothelial cell-extracellular matrix adhesion molecules, by antagonizing the function of angiogenesis inducers such as growth factors, and inhibiting integrin receptors expressed on proliferating endothelial cells. Examples of anti-angiogenic inhibitors that interfere with extracellular matrix proteolysis and which may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, AG-3340 (Agouron, La Jolla, Calif.), BAY-12-9566 (Bayer, West Haven, Conn.), BMS-275291 (Bristol Myers Squibb, Princeton, N.J.), CGS-27032A (Novartis, East Hanover, N.J.), Marimastat (British Biotech, Oxford, UK), and Metastat (Aeterna, St-Foy, Quebec). Examples of anti-angiogenic inhibitors that act by blocking the function of endothelial cell-extracellular matrix adhesion molecules and which may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, EMD-121974 (Merck KgaA Darmstadt, Germany) and Vitaxin (Ixsys, La Jolla, Calif./Medimmune, Gaithersburg, Md.). Examples of anti-angiogenic agents that act by directly antagonizing or inhibiting angiogenesis inducers and which may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, Angiozyme (Ribozyme, Boulder, Colo.), Anti-VEGF antibody (Genentech, S. San Francisco, Calif.), PTK-787/ZK-225846 (Novartis, Basel, Switzerland), SU-101 (Sugen, S. San Francisco, Calif.), SU-5416 (Sugen/Pharmacia Upjohn, Bridgewater, N.J.), and SU-6668 (Sugen). Other anti-angiogenic agents act to indirectly inhibit angiogenesis. Examples of indirect inhibitors of angiogenesis which may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, IM-862 (Cytan, Kirkland, Wash.), Interferon-alpha, IL-12 (Roche, Nutley, N.J.), and Pentosan polysulfate (Georgetown University, Washington, D.C.).

In particular embodiments, the use of antibody and antibody compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of an autoimmune disease, such as for example, an autoimmune disease described herein.

In a particular embodiment, the use of antibody and antibody compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of arthritis. In a more particular embodiment, the use of antibody and antibody compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of rheumatoid arthritis.

In another embodiment, antibody and antibody compositions of the invention are administered in combination with an anticoagulant. Anticoagulants that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, heparin, warfarin, and aspirin. In a specific embodiment, antibody and antibody compositions of the invention are administered in combination with heparin and/or warfarin. In another specific embodiment, antibody and antibody compositions of the invention are administered in combination with warfarin. In another specific embodiment, antibody and antibody compositions of the invention are administered in combination with warfarin and aspirin. In another specific embodiment, antibody and antibody compositions of the invention are administered in combination with heparin. In another specific embodiment, antibody and antibody compositions of the invention are administered in combination with heparin and aspirin.

In another embodiment, antibody and antibody compositions of the invention are administered in combination with an agent that suppresses the production of anticardiolipin antibodies. In specific embodiments, the polynucleotides of the invention are administered in combination with an agent that blocks and/or reduces the ability of anticardiolipin antibodies to bind phospholipid-binding plasma protein beta 2-glycoprotein I (b2GPI).

In certain embodiments, antibody and antibody compositions of the invention are administered in combination with antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors. Nucleoside reverse transcriptase inhibitors that may be administered in combination with the antibody and antibody compositions of the invention, include, but are not limited to, RETROVIR™ (zidovudine/AZT), VIDEX™ (didanosine/ddI), HIVID™ (zalcitabine/ddC), ZERIT™ (stavudine/d4T), EPIVIR™ (lamivudine/3TC), and COMBIVIR™ (zidovudine/lamivudine). Non-nucleoside reverse transcriptase inhibitors that may be administered in combination with the antibody and antibody compositions of the invention, include, but are not limited to, VIRAMUNE™ (nevirapine), RESCRIPTOR™ (delavirdine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with the antibody and antibody compositions of the invention, include, but are not limited to, CRIVANT™ (indinavir), NORVIR™ (ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in any combination with antibody and antibody compositions of the invention to treat, prevent, and/or diagnose AIDS and/or to treat, prevent, and/or diagnose HIV infection.

In other embodiments, antibody and antibody compositions of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the antibody and antibody compositions of the invention, include, but are not limited to, TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMYCIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™, FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICLOVIR™, PYRIMETHAMINE™, LEUCOVORIN™, NEUPOGEN™ (filgrastin/G-CSF), and LEUKINE™ (sargramostim/GM-CSF). In a specific embodiment, antibody and antibody compositions of the invention are used in any combination with TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, and/or ATOVAQUONE™ to prophylactically treat, prevent, and/or diagnose an opportunistic *Pneumocystis carinii* pneumonia infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, and/or ETHAMBUTOL™ to prophylactically treat, prevent, and/or diagnose an opportunistic *Mycobacterium avium* complex infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with RIFABUTIN™, CLARITHROMYCIN™, and/or AZITHROMYCIN™ to prophylactically treat, prevent, and/or diagnose an opportunistic *Mycobacterium tuberculosis* infection. In another specific embodiment, antibody and antibody compositions of the

invention are used in any combination with GANCICLOVIR™, FOSCARNET™, and/or CIDOFOVIR™ to prophylactically treat, prevent, and/or diagnose an opportunistic cytomegalovirus infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with FLUCONAZOLE™, ITRACONAZOLE™, and/or KETOCONAZOLE™ to prophylactically treat, prevent, and/or diagnose an opportunistic fungal infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with ACYCLOVIR™ and/or FAMCICLOVIR™ to prophylactically treat, prevent, and/or diagnose an opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with PYRIMETHAMINE™ and/or LEUCOVORIN™ to prophylactically treat, prevent, and/or diagnose an opportunistic *Toxoplasma gondii* infection. In another specific embodiment, antibody and antibody compositions of the invention are used in any combination with LEUCOVORIN™ and/or NEUPOGEN™ to prophylactically treat, prevent, and/or diagnose an opportunistic bacterial infection.

In a further embodiment, the antibody and antibody compositions of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, acyclovir, ribavirin, amantadine, and remantidine.

In a further embodiment, the antibody and antibody compositions of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, amoxicillin, aminoglycosides, beta-lactam (glycopeptide), beta-lactamases, Clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, ciprofloxacin, erythromycin, fluoroquinolones, macrolides, metronidazole, penicilins, quinolones, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamethoxazole, and vancomycin.

Conventional nonspecific immunosuppressive agents, that may be administered in combination with the antibody and antibody compositions of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs cyclophosphamide, cyclophosphamide IV, methylprednisolone, prednisolone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells.

In specific embodiments, antibody and antibody compositions of the invention are administered in combination with immunosuppressants. Immunosuppressants preparations that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, ORTHOCLONE™ (OKT3), SANDIMMUNE™/NEORAL™/SANGDYA™ (cyclosporin), PROGRAF™ (tacrolimus), CELLCEPT™ (mycophenolate), Azathioprine, glucorticosteroids, and RAPAMUNE™ (sirolimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with steroid therapy. Steroids that may be administered in combination with the antibody and antibody compositions of the invention, include, but are not limited to, oral corticosteroids, prednisone, and methylprednisolone (e.g., IV methylprednisolone). In a specific embodiment, antibody and antibody compositions of the invention are administered in combination with prednisone. In a further specific embodi-

ment, the antibody and antibody compositions of the invention are administered in combination with prednisone and an immunosuppressive agent. Immunosuppressive agents that may be administered with the antibody and antibody compositions of the invention and prednisone are those described herein, and include, but are not limited to, azathioprine, cyclophosphamide, and cyclophosphamide IV. In another specific embodiment, antibody and antibody compositions of the invention are administered in combination with methylprednisolone. In a further specific embodiment, the antibody and antibody compositions of the invention are administered in combination with methylprednisolone and an immunosuppressive agent. Immunosuppressive agents that may be administered with the antibody and antibody compositions of the invention and methylprednisolone are those described herein, and include, but are not limited to, azathioprine, cyclophosphamide, and cyclophosphamide IV.

In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with an antimalarial. Antimalarials that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, hydroxychloroquine, chloroquine, and/or quinacrine.

In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with an NSAID.

In a nonexclusive embodiment, the antibody and antibody compositions of the invention are administered in combination with one, two, three, four, five, ten, or more of the following drugs: NRD-101 (Hoechst Marion Roussel), diclofenac (Dimethaid), oxaprozin potassium (Monsanto), mecaseprin (Chiron), T-614 (Toyama), pemetrexed disodium (Eli Lilly), atreleuton (Abbott), valdecoxib (Monsanto), eltenac (Byk Gulden), campath, AGM-1470 (Takeda), CDP-571 (Celltech Chiroscience), CM-101 (CarboMed), ML3000 (Merckle), CB-2431 (KS Biomedix), CBF-BS2 (KS Biomedix), IL-1Ra gene therapy (Valentis), JTE-522 (Japan Tobacco), paclitaxel (Angiotech), DW-166HC (Dong Wha), darbufelone mesylate (Warner-Lambert), soluble TNF receptor 1 (synergen; Amgen), IPR-6001 (Institute for Pharmaceutical Research), trocade (Hoffman-La Roche), EF-5 (Scotia Pharmaceuticals), BIL-284 (Boehringer Ingelheim), BILF-1149 (Boehringer Ingelheim), LeukoVax (Inflammatics), MK-663 (Merck), ST-1482 (Sigma-Tau), and butixocort propionate (Warner Lambert).

In a preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with one, two, three, four, five or more of the following drugs: methotrexate, sulfasalazine, sodium aurothiomalate, auranofin, cyclosporine, penicillamine, azathioprine, an antimalarial drug (e.g., as described herein), cyclophosphamide, chlorambucil, gold, ENBREL™ (Etanercept), anti-TNF antibody, LJP 394 (La Jolla Pharmaceutical Company, San Diego, Calif.) and prednisolone.

In a more preferred embodiment, the antibody and antibody compositions of the invention are administered in combination with an antimalarial, methotrexate, anti-TNF antibody, ENBREL™ and/or sulfasalazine. In one embodiment, the antibody and antibody compositions of the invention are administered in combination with methotrexate. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with anti-TNF antibody. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with methotrexate and anti-TNF antibody. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with sulfasalazine.

In another specific embodiment, the antibody and antibody compositions of the invention are administered in combination with methotrexate, anti-TNF antibody, and sufasalazine. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with ENBREL™. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with ENBREL™ and methotrexate. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with ENBREL™, methotrexate and sufasalazine. In another embodiment, the antibody and antibody compositions of the invention are administered in combination with ENBREL™, methotrexate and sufasalazine. In other embodiments, one or more anti-malarials is combined with one of the above-recited combinations. In a specific embodiment, the antibody and antibody compositions of the invention are administered in combination with an antimalarial (e.g., hydroxychloroquine), ENBREL™, methotrexate and sufasalazine. In another specific embodiment, the antibody and antibody compositions of the invention are administered in combination with an antimalarial (e.g., hydroxychloroquine), sufasalazine, anti-TNF antibody, and methotrexate.

In an additional embodiment, antibody and antibody compositions of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the antibody and antibody compositions of the invention include, but not limited to, GAMMARTM, IVEEGAM™, SANDOGLOBULIN™, GAMMAGARD S/D™, and GAMIMUNE™. In a specific embodiment, antibody and antibody compositions of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

CD40 ligand (CD40L), a soluble form of CD40L (e.g., AVREND™), biologically active fragments, variants, or derivatives of CD40L, anti-CD40L antibodies (e.g., agonistic or antagonistic antibodies), and/or anti-CD40 antibodies (e.g., agonistic or antagonistic antibodies).

In an additional embodiment, the antibody and antibody compositions of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, glucocorticoids and the nonsteroidal anti-inflammatories, aminoarylcarboxylic acid derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzylamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole, and tenidap.

In another embodiment, compositions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, antibiotic derivatives (e.g., doxorubicin, bleomycin, daunorubicin, and dactinomycin); antiestrogens (e.g., tamoxifen); antimetabolites (e.g., fluorouracil, 5-FU, methotrexate, floxuridine, interferon alpha-2b, glutamic acid, plicamycin, mercaptopurine, and 6-thioguanine); cytotoxic agents (e.g., camustine, BCNU, lomustine, CCNU, cytosine arabinoside, cyclophosphamide, estiatustine, hydroxyurea,

procarbazine, mitomycin, busulfan, cis-platin, and vincristine sulfate); hormones (e.g., medroxyprogesterone, estramustine phosphate sodium, ethinyl estradiol, estradiol, megestrol acetate, methyltestosterone, diethylstilbestrol diphosphate, chlorotrianisene, and testolactone); nitrogen mustard derivatives (e.g., mephalen, chlorambucil, mechlorethamine (nitrogen mustard) and thiotepe); steroids and combinations (e.g., bethamethasone sodium phosphate); and others (e.g., dicarbazine, asparaginase, mitotane, vincristine sulfate, vinblastine sulfate, and etoposide).

In a specific embodiment, antibody and antibody compositions of the invention are administered in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or any combination of the components of CHOP. In another embodiment, antibody and antibody compositions of the invention are administered in combination with Rituximab. In a further embodiment, antibody and antibody compositions of the invention are administered with Rituximab and CHOP, or Rituximab and any combination of the components of CHOP.

In an additional embodiment, the antibody and antibody compositions of the invention are administered in combination with cytokines. Cytokines that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, GM-CSF, G-CSF, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-alpha, IFN-beta, IFN-gamma, TNF-alpha, and TNF-beta. In preferred embodiments, antibody and antibody compositions of the invention are administered with B Lymphocyte Stimulator (e.g., amino acids 134-285 of SEQ ID NO:3228). In another embodiment, antibody and antibody compositions of the invention may be administered with any interleukin, including, but not limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, IL-21, and IL-22. In preferred embodiments, the antibody and antibody compositions of the invention are administered in combination with IL4 and IL10.

In one embodiment, the antibody and antibody compositions of the invention are administered in combination with one or more chemokines. In specific embodiments, the antibody and antibody compositions of the invention are administered in combination with an α (C \times C) chemokine selected from the group consisting of gamma-interferon inducible protein-10 (IIP-10), interleukin-8 (IL-8), platelet factor-4 (PF4), neutrophil activating protein (NAP-2), GRO- α , GRO- β , GRO- γ , neutrophil-activating peptide (ENA-78), granulocyte chemoattractant protein-2 (GCP-2), and stromal cell-derived factor-1 (SDF-1, or pre-B cell stimulatory factor (PBSF)); and/or a β (CC) chemokine selected from the group consisting of: RANTES (regulated on activation, normal T expressed and secreted), macrophage inflammatory protein-1 alpha (MIP-1 α), macrophage inflammatory protein-1 beta (MIP-1 β), monocyte chemotactic protein-1 (MCP-1), monocyte chemotactic protein-2 (MCP-2), monocyte chemotactic protein-3 (MCP-3), monocyte chemotactic protein-4 (MCP-4), macrophage inflammatory protein-1 gamma (MIP-1 γ), macrophage inflammatory protein-3 alpha (MIP-3 α), macrophage inflammatory protein-3 beta (MIP-3 β), macrophage inflammatory protein A (MIP-4/DC-CK-1/PARC), eotaxin, Exodus, and I-309; and/or the γ (C) chemokine, lymphotactin.

In another embodiment, the antibody and antibody compositions of the invention are administered with chemokine beta-8, chemokine beta-1, and/or macrophage inflammatory

protein-4. In a preferred embodiment, the antibody and antibody compositions of the invention are administered with chemokine beta-8.

In an additional embodiment, the antibody and antibody compositions of the invention are administered in combination with an IL-4 antagonist. IL-4 antagonists that may be administered with the antibody and antibody compositions of the invention include, but are not limited to: soluble IL-4 receptor polypeptides, multimeric forms of soluble IL-4 receptor polypeptides; anti-IL4 receptor antibodies that bind the IL-4 receptor without balancing the biological signal elicited by IL-4, anti-IL-4 antibodies that block binding of IL-4 to one or more IL-4 receptors, and muteins of IL-4 that bind IL-4 receptors but do not transduce the biological signal elicited by IL-4. Preferably, the antibodies employed according to this method are monoclonal antibodies (including antibody fragments, such as, for example, those described herein).

The invention also encompasses combining the polynucleotides and/or polypeptides of the invention (and/or agonists or antagonists thereof) with other proposed or conventional hematopoietic therapies. Thus, for example, the polynucleotides and/or polypeptides of the invention (and/or agonists or antagonists thereof) can be combined with compounds that singly exhibit erythropoietic stimulatory effects, such as erythropoietin, testosterone, progenitor cell stimulators, insulin-like growth factor, prostaglandins, serotonin, cyclic AMP, prolactin, and triiodothyronine. Also encompassed are combinations of the antibody and antibody compositions of the invention with compounds generally used to treat aplastic anemia, such as, for example, methenolene, stanozolol, and nandrolone; to treat iron-deficiency anemia, such as, for example, iron preparations; to treat malignant anemia, such as, for example, vitamin B₁₂ and/or folic acid; and to treat hemolytic anemia, such as, for example, adrenocortical steroids, e.g., corticoids. See e.g., Resegotti et al., *Panminerva Medica*, 23:243-248 (1981); Kurtz, *FEBS Letters*, 14a:105-108 (1982); McGonigle et al., *Kidney Int.*, 25:437-444 (1984); and Pavlovic-Kantera, *Expt. Hematol.*, 8(supp. 8) 283-291 (1980), the contents of each of which are hereby incorporated by reference in their entireties.

Compounds that enhance the effects of or synergize with erythropoietin are also useful as adjuvants herein, and include but are not limited to, adrenergic agonists, thyroid hormones, androgens, hepatic erythropoietic factors, erythrotropins, and erythrogenins. See for e.g., Dunn, "Current Concepts in Erythropoiesis", John Wiley and Sons (Chichester, England, 1983); Kalmann, *Kidney Int.*, 22:383-391 (1982); Shahidi *New Eng. J. Med.*, 289:72-80 (1973); Umbe et al., *J. Exp. Med.*, 149:1314-1325 (1979); Biliat et al., *Expt. Hematol.*, 10:133-140 (1982); Naughton et al., *Acta Haemat.*, 69:171-179 (1983); Cognote et al. in abstract 364, *Proceedings 7th Intl. Cong. of Endocrinology* (Quebec City, Quebec, July 1-7, 1984); and Rothman et al., 1982, *J. Surg. Oncol.*, 20:105-108 (1982). Methods for stimulating hematopoiesis comprise administering a hematopoietically effective amount (i.e., an amount which effects the formation of blood cells) of a pharmaceutical composition containing polynucleotides and/or polypeptides of the invention (and/or agonists or antagonists thereof) to a patient. The polynucleotides and/or polypeptides of the invention and/or agonists or antagonists thereof is administered to the patient by any suitable technique, including but not limited to, parenteral, sublingual, topical, intrapulmonary and intranasal, and those techniques further discussed herein. The pharmaceutical composition optionally contains one or more members of the group consisting of erythropoietin, testosterone, progenitor cell stimulators, insulin-like growth factor, prostaglandins, serotonin, cyclic AMP,

prolactin, triiodothyronine, methenolene, stanozolol, and nandrolone, iron preparations, vitamin B₁₂, folic acid and/or adrenocortical steroids.

In an additional embodiment, the antibody and antibody compositions of the invention are administered in combination with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, LEUKINE™ (SARGRAMOSTIM™) and NEUPOGEN™ (FILGRASTIM™).

In an additional embodiment, the antibody and antibody compositions of the invention are administered in combination with fibroblast growth factors. Fibroblast growth factors that may be administered with the antibody and antibody compositions of the invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

Additionally, the antibody and antibody compositions of the invention may be administered alone or in combination with other therapeutic regimens, including but not limited to, radiation therapy. Such combinatorial therapy may be administered sequentially and/or concomitantly.

Kits

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In an alternative embodiment a kit comprises an antibody fragment that immunospecifically binds to B Lymphocyte Stimulator. In a specific embodiment, the kits of the present invention contain a substantially isolated B Lymphocyte Stimulator polypeptide as a control. Preferably, the kits of the present invention further comprise a control antibody which does not react with B Lymphocyte Stimulator. In another specific embodiment the kits of the present invention contain a means for detecting the binding of an antibody to B Lymphocyte Stimulator (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized B Lymphocyte Stimulator. The B Lymphocyte Stimulator provided in the kit may also be attached to a solid support. In a more specific embodiment the detecting means of the above-described kit includes a solid support to which B Lymphocyte Stimulator is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to B Lymphocyte Stimulator can be detected by binding of the said reporter-labeled antibody.

In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with B Lymphocyte Stimulator, and means for detecting the binding of B Lymphocyte Stimulator to the antibody. In one

embodiment the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound B Lymphocyte Stimulator obtained by the methods of the present invention. After B Lymphocyte Stimulator binds to a specific antibody, the unbound serum components are removed by washing, reporter-labeled anti-human antibody is added, unbound anti-human antibody is removed by washing, and a reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-B Lymphocyte Stimulator antibody on the solid support. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate.

The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface-bound recombinant B Lymphocyte Stimulator, and a reporter-labeled anti-human antibody for detecting surface-bound anti-B Lymphocyte Stimulator antibody.

In specific embodiments, the present invention encompasses a single chain Fv (scFv) having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention encompasses a single chain Fv (scFv) having an amino acid sequence of one of SEQ ID NOS: 1 to 46, 321 to 329, 1563 to 1595, and 1881 to 1908.

In specific embodiments, the present invention encompasses a single chain Fv (scFv) having an amino acid sequence of one of SEQ ID NOS: 1563 to 1880.

In specific embodiments, the present invention encompasses a single chain Fv (scFv) having an amino acid sequence of one of SEQ ID NOS: 1881 to 2128.

In specific embodiments, the present invention encompasses a single chain Fv (scFv) having an amino acid sequence of one of SEQ ID NOS: 1 to 1562.

In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator.

In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 46, 321 to 329, 1563 to 1595, and 1881 to 1908.

In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1881 to 2128, and in which said antibody or

fragment thereof immunospecifically binds to the membrane-bound form of B Lymphocyte Stimulator.

In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1563 to 1880, and in which said antibody or fragment thereof immunospecifically binds to the soluble form of B Lymphocyte Stimulator.

In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator.

In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 46, 321 to 329, 1563 to 1595, and 1881 to 1908.

In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1881 to 2128, and in which said antibody or fragment thereof immunospecifically binds to the membrane-bound form of B Lymphocyte Stimulator.

In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1563 to 1880, and in which said antibody or fragment thereof immunospecifically binds to the soluble form of B Lymphocyte Stimulator.

In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128 and in which said VL and said VH domains are derived from the same scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention encompasses an antibody or fragment thereof comprising an amino acid sequence of one of SEQ ID NOS: 2129 to 3227 wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator.

In specific embodiments, the antibody or fragment thereof of the invention is a whole immunoglobulin molecule.

In specific embodiments, the antibody or fragment thereof of the invention is a Fab fragment.

In specific embodiments, the antibody or fragment thereof of the invention is a Fv fragment.

In specific embodiments, the present invention encompasses a chimeric protein comprising the antibody or fragment thereof of the invention covalently linked to a heterologous polypeptide.

In specific embodiments, the present invention encompasses a composition comprising two or more types of antibodies or fragments or variants thereof, each of which type

immunospecifically binds to B Lymphocyte Stimulator, and each of which type of antibody or fragment thereof comprises a VH domain from a different scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention encompasses a composition comprising two or more types of antibodies or fragments or variants thereof, each of which type immunospecifically binds to B Lymphocyte Stimulator, and each of which type of antibody or fragment thereof comprises a VL domain from a different scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention encompasses a composition comprising two or more types of antibodies or fragments or variants thereof, each of which type immunospecifically binds to B Lymphocyte Stimulator, and each of which type of antibody or fragment thereof comprises a VL domain from a different scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128 and wherein each type of antibody or fragment thereof further comprises a VH domain from a different scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention encompasses a composition comprising two or more types of antibodies or fragments or variants thereof, each of which type immunospecifically binds to B Lymphocyte Stimulator, and each of which type of antibody or fragment thereof comprises a VH CDR3 having an amino acid sequence of one of SEQ ID NOS: 3129 to 3227.

In specific embodiments, the present invention encompasses a panel of two or more types of antibodies or fragments or variants thereof, each of which type immunospecifically binds to B Lymphocyte Stimulator, and each of which type of antibody or fragment thereof comprises a VH domain from a different scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention encompasses a panel of two or more types of antibodies or fragments or variants thereof, each of which type immunospecifically binds to B Lymphocyte Stimulator, and each of which type of antibody or fragment thereof comprises a VL domain from a different scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention encompasses a panel of two or more types of antibodies or fragments or variants thereof, each of which type immunospecifically binds to B Lymphocyte Stimulator, and each of which type of antibody or fragment thereof comprises a VL domain from a different scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128 and wherein each type of antibody or fragment further comprises a VH domain from a different scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention encompasses a panel of two or more antibodies or fragments or variants thereof, each of which type immunospecifically binds to B Lymphocyte Stimulator, and each of which type of antibody or fragment thereof comprises a VHCDR3 from a different scFv having an amino acid sequence of one of SEQ ID NOS: 2129 to 3227.

In specific embodiments, the antibodies or fragments thereof of the antibody panel of the invention, are each in a well of a 96 well plate.

In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid

sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator.

In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 46, 321 to 329, 1563 to 1595, and 1881 to 1908, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator.

In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1881 to 1908, wherein the antibody of fragment thereof immunospecifically binds the membrane-bound form of B Lymphocyte Stimulator.

In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1563 to 1569, wherein said antibody or fragment thereof immunospecifically binds the soluble form of B Lymphocyte Stimulator. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 46, 321 to 329, 1563 to 1595, and 1881 to 1908, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator.

The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1881 to 2128, wherein the antibody or fragment thereof immunospecifically binds the membrane-bound form of B Lymphocyte Stimulator. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1563 to 1880, wherein said antibody or fragment thereof immunospecifically binds the soluble form of B Lymphocyte Stimulator. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide

sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128 and in which said VL domain and said VH domain are derived from the same scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

In specific embodiments, the present invention encompasses an isolated nucleic acid molecule comprising a nucleotide sequence encoding an antibody or fragment thereof comprising a VHCDR3 from an scFv having an amino acid sequence of one of SEQ ID NOS: 2129 to 3227, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator. The present invention also encompasses vectors comprising the isolated nucleic acid molecule described above, including vectors comprising a nucleotide sequence which regulates the expression of the antibody or fragment thereof encoded by the above-described nucleic acid molecule. Additionally the present invention also encompasses host cells, including mammalian host cells, comprising the above-described nucleic acid molecule which is operably linked to a heterologous promoter, as well as host cells, including mammalian host cells, comprising the above-described vectors. Additionally, the present invention also provides a method for producing an antibody or fragment thereof comprising culturing the above-described host cells under conditions in which the nucleic acid molecule is expressed.

In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to B Lymphocyte Stimulator, said antibody or fragment thereof comprising an amino acid sequence of a VH domain encoded by a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence encoding a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to B Lymphocyte Stimulator, said antibody or fragment thereof comprising an amino acid sequence of a VL domain encoded by a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence encoding a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to B Lymphocyte Stimulator, said antibody or fragment thereof comprising an amino acid sequence of a VH domain encoded by a nucleotide sequence that hybridizes under highly stringent conditions to a nucleotide sequence encoding a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to B Lymphocyte Stimulator, said antibody or fragment thereof comprising an amino acid sequence of a VL domain encoded by a nucleotide sequence that hybridizes under highly stringent conditions to a nucleotide sequence encoding a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to B Lymphocyte Stimulator, said antibody or fragment thereof comprising an amino acid sequence of a CDR encoded by a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence encoding a CDR from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to B Lymphocyte Stimulator, said antibody or fragment thereof comprising an amino acid sequence of a CDR encoded by a nucleotide sequence that hybridizes under highly stringent conditions to a nucleotide sequence encoding a CDR from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to B Lymphocyte Stimulator, said antibody or fragment thereof comprising an amino acid sequence of a VH CDR3 encoded by a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence encoding a VH CDR3 having an amino acid sequence of one of SEQ ID NOS: 2129 to 3227.

In specific embodiments, the present invention provides an antibody or fragment thereof that immunospecifically binds to B Lymphocyte Stimulator, said antibody or fragment thereof comprising an amino acid sequence of a VR CDR3 encoded by a nucleotide sequence that hybridizes under highly stringent conditions to a nucleotide sequence encoding a VH CDR3 having an amino acid sequence of one of SEQ ID NOS: 2129 to 3227.

In specific embodiments, the present invention provides a method for detecting of aberrant expression of B Lymphocyte Stimulator, comprising:

assaying the level of B Lymphocyte Stimulator expression in cells or a tissue sample of an individual using one or more antibodies or fragments or variants thereof that immunospecifically bind B Lymphocyte Stimulator, and

comparing the level of B Lymphocyte Stimulator assayed in the cells or a tissue sample with a standard level of B Lymphocyte Stimulator or a level of B Lymphocyte Stimulator in cells or a tissue sample from an individual without

aberrant B Lymphocyte Stimulator expression, wherein an increase or decrease in the assayed level of B Lymphocyte Stimulator or level in cells or a tissue sample from an individual without aberrant B Lymphocyte Stimulator expression compared to the standard level of B Lymphocyte Stimulator is indicative of aberrant expression.

In specific embodiments, the present invention provides a method for diagnosing a disease or disorder associated with aberrant B Lymphocyte Stimulator expression or activity, comprising:

administering to a subject an effective amount of a labeled antibody or fragment thereof that immunospecifically binds to B Lymphocyte Stimulator;

waiting for a time interval following the administering for permitting the labeled antibody or fragment thereof to preferentially concentrate at sites in the subject where B Lymphocyte Stimulator is expressed;

determining background level; and

detecting the labeled antibody or fragment thereof in the subject, such that detection of labeled antibody or fragment thereof above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of B Lymphocyte Stimulator.

In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above comprises a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128.

In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above comprises a VH CDR3 having an amino acid sequence of one of SEQ ID NOS: 2129 to 3227.

In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above is conjugated to a diagnostic agent.

In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above is conjugated to a diagnostic agent wherein the diagnostic agent is horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase.

In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above is conjugated to a diagnostic agent wherein the diagnostic agent is fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin.

In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above is conjugated to a diagnostic agent wherein the diagnostic agent is ^{125}I , ^{131}I , ^{111}In , ^{90}Y or ^{99}Tc .

In specific embodiments, the antibody or fragment thereof utilized in the two methods described immediately above is conjugated to a diagnostic agent wherein the diagnostic agent is luciferase, luciferin or aequorin.

A pharmaceutical composition comprising at least one antibody or fragment thereof of comprising a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator and a pharmaceutically acceptable carrier.

A pharmaceutical composition comprising at least one antibody or fragment thereof of comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof

immunospecifically binds B Lymphocyte Stimulator and a pharmaceutically acceptable carrier.

A pharmaceutical composition comprising at least one antibody or fragment thereof of comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128 and a pharmaceutically acceptable carrier.

A pharmaceutical composition comprising at least one antibody or fragment thereof of comprising an amino acid sequence of one of SEQ ID NOS: 2129 to 3227 wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator and a pharmaceutically acceptable carrier.

A method of treating, preventing or ameliorating a disease or disorder associated with aberrant B Lymphocyte Stimulator expression or activity, comprising administering to an animal in need thereof the pharmaceutical composition comprising at least one antibody or fragment thereof of comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128 and a pharmaceutically acceptable carrier in an amount effective to treat, prevent or ameliorate the disease or disorder. This method may be used to treat an infectious disorder, cancer, and/or an autoimmune disease such as lupus or glomerular nephritis.

A method of treating, preventing or ameliorating a disease or disorder associated with aberrant B Lymphocyte Stimulator expression or activity, comprising administering to an animal in need thereof the pharmaceutical composition comprising at least one antibody or fragment thereof of comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator and a pharmaceutically acceptable carrier in an amount effective to treat, prevent or ameliorate the disease or disorder. This method may be used to treat an infectious disorder, cancer, and/or an autoimmune disease such as lupus or glomerular nephritis.

A method of treating, preventing or ameliorating a disease or disorder associated with aberrant B Lymphocyte Stimulator expression or activity, comprising administering to an animal in need thereof the pharmaceutical composition comprising at least one antibody or fragment thereof of comprising a VL domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128, wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator and which also comprises a VH domain from an scFv having an amino acid sequence of one of SEQ ID NOS: 1 to 2128 and a pharmaceutically acceptable carrier in an amount effective to treat, prevent or ameliorate the disease or disorder. This method may be used to treat an infectious disorder, cancer, and/or an autoimmune disease such as lupus or glomerular nephritis.

A method of treating, preventing or ameliorating a disease or disorder associated with aberrant B Lymphocyte Stimulator expression or activity, comprising administering to an animal in need thereof the pharmaceutical composition of comprising at least one antibody or fragment thereof of comprising an amino acid sequence of one of SEQ ID NOS: 2129 to 3227 wherein said antibody or fragment thereof immunospecifically binds B Lymphocyte Stimulator and a pharmaceutically acceptable carrier in an amount effective to treat, prevent or ameliorate the disease or disorder. This method may be used to treat an infectious disorder, cancer, and/or an autoimmune disease such as lupus or glomerular nephritis.

aceutically acceptable carrier in an amount effective to treat, prevent or ameliorate the disease or disorder. This method may be used to treat an infectious disorder, cancer, and/or an autoimmune disease such as lupus or glomerular nephritis.

This method may be used to treat an infectious disorder, cancer, and/or an autoimmune disease such as lupus or glomerular nephritis.

EXAMPLES

Abbreviations

0.2 M Tris-HCl, 0.5 mM EDTA, 0.5 M sucrose (TES)
1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (EDC)
2TY supplemented with 100 µg/ml ampicillin and 2% glucose (2TYAG)
2TY supplemented with 100 µg/ml ampicillin and 50 µg/ml kanamycin (2TYAK)
3,3',5,5'-Tetramethyl Benzidine (TMB)
50% inhibitory concentration (IC₅₀)
6×PBS containing 18% Marvel blocking solution (6×MPBS)
Absorbance (A)
Bovine serum albumin (BSA)
Enzyme linked immunosorbent assay (ELISA)
Foetal calf serum (FCS)
Heavy chain variable (VH)
Hepes buffered saline (HBS)
Horseradish peroxidase (HRP)
Immobilised Metal Affinity Chromatography (IMAC)
Isopropyl β-D-thiogalactopyranoside (IPTG)
Light chain variable (VL)
Multiplicity of infection (MOI)
N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid] (Hepes)
Nanomolar (nM)
N-Hydroxysuccinimide (NHS)
PBS containing 3% Marvel (MPBS)
Phosphate Buffered Saline (PBS)
Phosphate Buffered Saline+0.1% (v/v) Tween 20 (PBST)
Picomolar (pM)
Single chain fragment variable (scFv)
Tumour Necrosis Factor-alpha (TNF-α)
Tumour Necrosis Factor-beta (TNF-β)
TNF-related apoptosis inducing ligand (TRAIL)

Definitions:

In the following section "immobilized B Lymphocyte Stimulator" refers to a soluble form of B Lymphocyte Stimulator or biotinylated B Lymphocyte Stimulator coated on a plastic assay plate (e.g., a 96 well plate), but does not refer to histidine tagged B Lymphocyte Stimulator coated on a plastic assay plate.; "biotinylated B Lymphocyte Stimulator" is a soluble form of B Lymphocyte Stimulator except when used to coat an ELISA plate, in which case it would be "immobilized B Lymphocyte Stimulator." Membrane bound forms of B Lymphocyte Stimulator include, but are not limited to, U937 and P388 plasma membranes.

Example 1

Antibodies Immunospecifically Binding to Soluble and Membrane-Bound B Lymphocyte Stimulator

A library of phage was screened in an assay to identify those phage displaying scFvs that immunospecifically bind to the soluble and membrane-bound forms of B Lymphocyte Stimulator. Phage displaying scFvs that bound to immobi-

lized B Lymphocyte Stimulator were identified after panning on immobilized B Lymphocyte Stimulator and assessment by ELISA for binding to immobilized B Lymphocyte Stimulator. The B Lymphocyte Stimulator that was immobilized on plates for these assays was purified from supernatants of Sf9 cells infected with a baculovirus expression construct as described in Moore et al., Science 285:260-263 which is hereby incorporated by reference in its entirety. Each of the identified scFvs were then sequenced. Certain sequences were isolated multiple times, thus a panel (panel 1) containing one member of each unique sequences was generated and further characterized for their ability to immunospecifically bind to the soluble and membrane-bound forms of B Lymphocyte Stimulator.

The derived amino acid sequences of these scFvs are shown in Table 1 above. The individual V_H and V_L segments of the scFvs were aligned to the known human germline sequences in V-BASE (Tomlinson et al, which can accessed on the United Kingdom Medical Research Council (MRC) Centre for Protein Engineering website) and the closest germline identified.

Example 2

Specificity of scFvs for B Lymphocyte Stimulator and Membrane-Bound B Lymphocyte Stimulator

The specificity of each of the scFvs for both B Lymphocyte Stimulator and membrane-bound B Lymphocyte Stimulator was determined by phage ELISA. B Lymphocyte Stimulator was immobilised onto plastic as a purified soluble form of the protein or as a membrane-bound form present on plasma membrane preparations from the human macrophage-like cell line, U937.

Maintenance of U937 Cells

U937 cells are a human monocyte-like, histiocytic lymphoma cell line known to express B Lymphocyte Stimulator on their plasma membranes. They were maintained in RPMI-1640 supplemented with 4 mM L-glutamine, 10% FCS, 10 U penicillin, 100 g/ml streptomycin (all reagents from Sigma). The cells were thawed from frozen stock and are either used for plasma membrane preparation, or split 1:5, after 2 days in culture when the cell density reaches 1×10^6 /ml.

Preparation of U937 Plasma Membranes

To prepare plasma membranes, 1×10^9 U937 cells were harvested from their culture medium by centrifugation at 1000 rpm at 4° C. for 5 minutes in a benchtop centrifuge. The cells were resuspended in 40 ml 12 mM Tris, pH 7.5, 250 mM sucrose and placed on ice. The cells are then lysed using a hand-held electric homogenizer (Labortechnik IKA Ultra-Tumax) for four, one minute, bursts. To check that cell lysis had occurred, 10 μ l cell lysate was added to 10 μ l Trypan blue and the cell lysate was examined under a microscope. After confirming lysis, the homogenate was centrifuged at 270 \times g, for 10 minutes at 4° C. to pellet the nuclear fraction and the supernatant was retained. The supernatant was centrifuged at 8000 \times g, 10 mins, 4° C., to pellet the mitochondrial and lysosomal fractions and the supernatant was retained. The supernatant was then centrifuged at 100000 \times g, 60 mins, 4° C. to pellet the plasma membrane enriched fraction. The supernatant was discarded and the plasma membrane pellet was resuspended in 1 ml PBS and stored at -70° C. The protein concentration of the plasma membrane fraction was determined using a protein quantification kit (Biorad). Typical yields were between 5 and 10 mg of plasma membranes.

Phage ELISA

To determine the specificity of each of the unique scFvs, a phage ELISA was performed for each scFv against human B Lymphocyte Stimulator, U937 plasma membranes, TNFA (R&D Systems, Minneapolis, Minn.), BSA and uncoated well. Individual *E. coli* colonies containing a phagemid representing one of the unique scFvs from panel 1 were inoculated into 96-well plates containing 100 μ l 2TYAG medium per well. Plates were incubated at 37° C. for 4 hours, shaking. M13KO7 helper phage was added to each well to a MOI of 10 and the plates were incubated for a further 1 hour at 37° C. The plates were centrifuged in a benchtop centrifuge at 2000 rpm for 10 minutes. The supernatant was removed and cell pellets were resuspended in 100 μ l 2TYAK and incubated at 30° C. overnight, shaking. The next day, plates were centrifuged at 2000 rpm for 10 min and the 100 μ l phage-containing supernatant from each well carefully transferred into a fresh 96-well plate. Twenty μ l of 6 \times MPBS was added to each well, and incubated at room temperature for 1 hour to pre-block the phage prior to ELISA.

Flexible 96-well plates (Falcon) were coated overnight at 4° C. with human B Lymphocyte Stimulator (1 μ g/ml) in PBS, U937 plasma membranes (10 μ g/ml) in PBS, TNF α (1 μ g/ml) in PBS, BSA (1 μ g/ml) in PBS, or PBS. After coating, the solutions were removed from the wells, and the plates were blocked for 1 hour at room temperature in MPBS. The plates were washed 3 times with PBS and then 50 μ l of pre-blocked phage was added to each well. The plates were incubated at room temperature for 1 hour and then washed with 3 changes of PBST followed by 3 changes of PBS. To each well, 50 μ l of an anti-gene VIII-HRP conjugate (Pharmacia) at a 1 to 5000 dilution in MPBS was added and the plates incubated at room temperature for 1 hour. Each plate was washed three times with PBST followed by three times with PBS. Then 50 μ l of an HRP-labelled anti-mouse polymer (DAKO EnVision) diluted 1/50 in 3% MPBS was added and incubated for 1 hour at room temperature. Each plate was then washed three times with PBST followed by three times with PBS. Fifty μ l of TMB substrate was then added to each well, and incubated at room temperature for 30 minutes or until colour development. The reaction was stopped by the addition of 25 μ l of 0.5 M H₂SO₄. The signal generated was measured by reading the absorbance at 450 nm (A_{450}) using a microtiter plate reader (Bio-Rad 3550).

The results for 3 clones (I006E07, I008D05 and I016F04) are shown in FIG. 1. All 3 scFvs recognize immobilized B Lymphocyte Stimulator and U937 plasma membranes but do not recognize TNF α , BSA or an uncoated well (PBS only). These results indicate that these scFvs specifically recognize immobilized B Lymphocyte Stimulator and membrane-bound B Lymphocyte Stimulator.

Example 3

Inhibition in an In Vitro Receptor Binding Assay by Phage scFvs

All of the unique phage scFvs in panel 1 were assessed for their ability to inhibit soluble B Lymphocyte Stimulator binding to its cognate receptor on IM9 cells.

Biotinylation of B Lymphocyte Stimulator

One hundred μ g of either human or mouse B Lymphocyte Stimulator was dialysed overnight at 4° C. against 50 mM sodium bicarbonate (sodium hydrogen carbonate) pH8.5 using a slide-a-lyzer cassette (Pierce). The next day, NHS-biotin (Pierce) was dissolved in DMSO to 13.3 mg/ml. This

was then added to the B Lymphocyte Stimulator at a molar ratio of 20:1 biotin:B Lymphocyte Stimulator, mixed and incubated on ice for 2 hours. The biotinylated B Lymphocyte Stimulator was then dialysed back into sterile PBS (Sigma) using a slide-a-lyzer cassette overnight at 4° C. The biological activity of the biotinylated B Lymphocyte Stimulator was confirmed using the receptor binding inhibition assay (see below).

Maintenance of IM49 Cells

IM9 cells are a human B lymphocyte cell line. They were maintained in RPMI-1640 supplemented with 4 mM L-glutamine, 10% FCS, 10 U penicillin, 100 g/ml streptomycin (all reagents from Sigma). The cells are thawed from frozen stock and can be used in assays after 5 days in culture when they reach a density of $4-8 \times 10^5$ /ml.

Receptor Binding Inhibition Assay

Individual *E. coli* colonies containing a phagemid representing one of the unique scFvs from panel 1 were inoculated into 96-well plates containing 100 μ l 2TYAG medium per well. Plates were incubated at 37° C. for 4 hours, shaking. M13KO7 helper phage was added to each well to a MOI of 10 and the plates were incubated for a further 1 hour at 37° C. The plates were centrifuged in a benchtop centrifuge at 2000 rpm for 10 minutes. The supernatant was removed and cell pellets were resuspended in 100 μ l 2TYAK and incubated at 30° C. overnight, shaking. The next day, plates were centrifuged at 2000 rpm for 10 min and the 100 μ l phage-containing supernatant from each well carefully transferred into a fresh 96-well plate. Phage were diluted 1 in 2 in MPBS prior to use.

Flat-bottomed 96-well plates (Costar) were coated with 100 μ l per well of a 1:10 dilution of poly-L-lysine (Sigma) in PBS for 1 hour at room temperature. The plates were then washed twice with water, allowed to air-dry and placed at 4° C. overnight. One hundred μ l of IM9 cells (at 10^6 /ml in RPMI-1640 culture medium) were then added to each well. Plates were then centrifuged at 3200 rpm for 5 mins to pellet the cells. The media was carefully aspirated and 200 μ l of MPBS added to each well. The plates were then allowed to block for 1 hour at room temperature.

To a separate 96-well plate 10 μ l of biotinylated B Lymphocyte Stimulator (at 162.5 ng/ml) in MPBS was added to each well to give a final concentration of 25 ng/ml. Fifty-five μ l of each appropriate phage supernatant was added to each well and the final volume in each well was 65 μ l. Plates were then incubated at room temperature for 30 minutes.

The IM9 coated plates were washed twice in PBS, tapped dry and immediately 50 μ l of the phage/biotinylated-B Lymphocyte Stimulator mix was added and incubated at room temperature for 1 hour. Plates were washed three times in PBST and three times in PBS, tapped dry and 50 μ l of streptavidin-Delfia (Wallac) was added to each well at 1:1000 dilution in the Manufacturer's assay buffer. The plates were then incubated at room temperature for 1 hour and washed six times in Delfia wash solution (Wallac). After tapping the plates dry, 100 μ l per well of Delfia enhancement solution (Wallac) was added. The plates were gently tapped to encourage micelle formation, incubated at room temperature for 10 minutes, and fluorescence read on a Wallac 1420 workstation at 6520 nM.

Results for 3 phage scFvs (I001C09, I018D07 and I016H07) that inhibited the binding of biotinylated B Lymphocyte Stimulator are shown in FIG. 2. Maximal binding of biotinylated B Lymphocyte Stimulator to its receptor (bio-B Lymphocyte Stimulator only), the background signal in the absence of biotinylated B Lymphocyte Stimulator (no bio-B Lymphocyte Stimulator), and results with an irrelevant (i.e.,

does not recognize B Lymphocyte Stimulator) phage antibody are also shown. All 3 phage scFvs inhibited biotinylated B Lymphocyte Stimulator binding to its receptor on IM9 cells, identifying these scFvs as scFvs that bind the soluble form of B Lymphocyte Stimulator. These scFvs also bind to U937 membranes, thus they also bind the membrane bound form of B Lymphocyte Stimulator.

Forty-eight of the scFvs from panel 1 that demonstrated the greatest inhibition as phage particles in this assay were chosen for further study. These 48 scFvs are listed in Table 3.

TABLE 3

scFvs that Inhibit the Binding of Biotinylated-B Lymphocyte Stimulator to its Receptor

Antibody	Antibody	Antibody	Antibody	Antibody
I008C02	I029D07	I008C03	I008C12	I028A06
I022E02	I061E07	I007H08	I061H01	I031C03
I018C02	I006D07	I008A11	I006D08	I031F02
I008B01	I017D10	I061D02	I026E03	I031F09
I016F04	I007B03	I008A09	I027A07	I031G11
I016E05	I018C10	I007F11	I016H07	I050A07
I018H08	I001C09	I037E07	I021B05	I050A12
I018H09	I018D07	I037E12	I031G10	I050B11
	I029F11	I016F02	I031G08	I051C04
	I022D01		I031C07	I003F12
			I012A06	

Example 4

Specificity of Anti-B Lymphocyte Stimulator Antibodies

The specificity of the 48 scFvs listed in Table 3 for human and murine B Lymphocyte Stimulator was determined using phage ELISA.

Phage ELISA

To determine the specificity of the 48 scFvs, a phage ELISA was performed against human and mouse B Lymphocyte Stimulator, and a panel of related and unrelated human antigens: Fas ligand, TRAIL, TNF α , TNF β , and PBS. The: Fas ligand, TRAIL, TNF α , and TNF β antigens were obtained from R&D Systems, Minneapolis, Minn. Individual *E. coli* colonies containing phagemid were inoculated into 5 ml 2TYAG and incubated at 37° C. for 4 hours, shaking. M13KO7 helper phage (Pharmacia) was added to each tube to a MOI of 10 and incubated for 30 minutes at 37° C. for 1 hour, the first 30 minutes static and the final 30 minutes with gentle shaking. Cells were pelleted by centrifugation at 3,500 rpm for 10 minutes and the supernatant discarded. Cell pellets were resuspended in 5 ml 2TYAK and incubated at 30° C. overnight with shaking. The next day, the cells were pelleted by centrifugation at 3,500 rpm for 10 minutes. The phage-containing supernatant (5 ml) was carefully transferred to a fresh tube, 1 ml of 6MPBS was added, and the tube was incubated at room temperature for 1 hour to pre-block the phage prior to ELISA.

All antigens were coated at 1 μ g/ml. ELISAs were performed essentially as described in Example 2. The only exception to this being the detection of phage antibody binding to mouse B Lymphocyte Stimulator where the step involving incubation with the HRP-labelled anti-mouse polymer was omitted. Binding to mouse B Lymphocyte Stimulator was detected with TMB as in Section Example 2.

All 48 scFvs are specific for immobilized human B Lymphocyte Stimulator and 43 out of the 48 scFvs cross-react

with immobilized mouse B Lymphocyte Stimulator but not with any other unrelated or related antigen tested. I008C03, I007F11, I037E07, I037E12, and I016H07 did not bind murine B Lymphocyte Stimulator. Results for two scFvs, I022D01 and I031F02, are shown in FIG. 3. Both these scFvs specifically recognize human and mouse B Lymphocyte Stimulator but not any other unrelated or related antigen tested.

Example 5

Specificity for the Membrane-Bound Form of B Lymphocyte Stimulator

The specificity of 48 scFvs for membrane-bound B Lymphocyte Stimulator was determined by the phage ELISA described in Example 2. B Lymphocyte Stimulator was immobilised onto plastic as a membrane-bound form present on plasma membranes preparations from the human macrophage-like cell line, U937. This cell line is known to express the membrane-bound form of human B Lymphocyte Stimulator.

To demonstrate that this binding is specific for membrane-bound B Lymphocyte Stimulator, a competition ELISA was developed to determine if the ELISA signal for an individual antibody on U937's could be competed out by pre-incubation with either B Lymphocyte Stimulator or TNF α . An anti-B Lymphocyte Stimulator antibody that also recognizes membrane-bound B Lymphocyte Stimulator would be expected to demonstrate a signal reduction with free B Lymphocyte Stimulator but not free TNF α .

Competition ELISA

Individual *E. coli* colonies containing phagemid for each of the 48 scFvs listed in Table 3 were inoculated into 5 ml 2YTAG and incubated at 37° C. for 4 hours, shaking. M13KO7 helperphage (Pharmacia) was added to each tube to a MOI of 10 and incubated for 30 minutes at 37° C. for 1 hour, the first 30 minutes static and the final 30 minutes with gentle shaking. Cells were pelleted by centrifugation at 3,500 rpm for 10 minutes and the supernatant discarded. Cell pellets were resuspended in 5 ml 2TYAK and incubated at 30° C. overnight with shaking. The next day, the cells were pelleted by centrifugation at 3,500 rpm for 10 minutes. The phage-containing supernatants (5 ml) were carefully transferred to a fresh tube.

For each of the 48 scFvs listed in Table 3, two aliquots of 20 μ l 6xMPBS were pipetted into separate wells of a 96-well plate (Greiner). The first aliquot was supplemented with B Lymphocyte Stimulator to a final concentration of 0.5 μ g/ml. The second aliquot was supplemented with TNF- α to a final concentration of 0.5 μ g/ml. Each experiment was performed in triplicate. One hundred μ l of each phage supernatant was then added to each aliquot and mixed by pipetting up and down. The phage were incubated (\pm competing antigen) at room temperature for 1 hour.

Flexible 96-well plates (Falcon) were coated overnight at 4° C. with 50 μ l of 10 μ g/ml U937 plasma membranes. After coating, the plates were washed 3 times with PBS and blocked for 1 hour at room temperature with 200 μ l MPBS. The plates were washed 3 times with PBS and 50 μ l of phage (\pm competing antigen) was added to each appropriate well. The plates were incubated at room temperature for 1 hour and then washed with 3 changes of PBST followed by 3 changes of PBS. To each well, 50 μ l of a mouse anti-gene VIII-HRP conjugate (Pharmacia) at a 1:5000 dilution in MPBS was added and the plates incubated at room temperature for 1

hour. Each plate was washed three times with PBST followed by three times with PBS. Then 50 μ l of an HRP-labelled anti-mouse polymer (DAKO EnVision) diluted 1:50 in 3% MPBS was added and incubated for 1 hour at room temperature. Each plate was then washed three times with PBST followed by three times with PBS. Fifty μ l of TMB substrate was then added to each well, and incubated at room temperature for 30 to 60 minutes or until color development. The reaction was stopped by the addition of 25 μ l of 0.5 M H₂SO₄. The signal generated was measured by reading the absorbance at 450 nm (A₄₅₀) using a microtiter plate reader (Bio-Rad 3550).

All 48 scFvs bind to U937 plasma membrane preparations. This signal could be competed out by pre-incubation of the phage antibody with B Lymphocyte Stimulator but not by pre-incubation with TNF- α . This indicates that the 48 scFvs specifically recognize membrane-bound B Lymphocyte Stimulator as well as soluble B Lymphocyte Stimulator. Typical results are exemplified by scFvs I031F09, I050A12 and I051C04 and are shown in FIG. 4. All 3 scFvs demonstrate binding to U937 plasma membranes. This binding was specifically competed out with B Lymphocyte Stimulator but did not compete with TNF- α , demonstrating specific recognition of membrane-bound B Lymphocyte Stimulator.

Example 6

scFv Off-Rate Determinations

All off-rate determinations were performed on BIAcore 2000 machines, using the BIAcore 2000 Control Software and evaluated using the BIAevaluation 3.0 software.

Preparation of a Low Density B Lymphocyte Stimulator Surface

A 500RU surface was prepared for kinetic studies with purified scFvs. A low density B Lymphocyte Stimulator surface (500 RU B Lymphocyte Stimulator coupled) was prepared in flow cell 2 by amine coupling to a CM5 chip. A new CM5 chip was inserted into the BIAcore and a sensorgram initiated with HBS buffer at a flow rate of 5 μ l/min. The NHS and EDC coupling solutions (BIAcore) were mixed according to manufacturer's instructions and 30 μ l injected over the CM5 surface. Fifty μ l of B Lymphocyte Stimulator at 1 μ g/ml in 10 mM sodium acetate buffer, pH4, was then injected followed by 30 μ l of ethanolamine-HCl solution (BIAcore). The flow rate was then adjusted to 20 μ l/min and 10 μ l of 4M guanidine hydrochloride in RBS injected over the surface. This strips the surface of non-covalently bound B Lymphocyte Stimulator.

Measurement of scFv Off-Rate Kinetics on the Low Density Surfaces

The chip containing the low density B Lymphocyte Stimulator surface was inserted in to the BIAcore. A dilution series of purified scFvs was prepared in HBS, typically 50 μ g/ml doubling dilutions down to 1.5 μ g/ml. The dilution series was then injected sequentially over the low density B Lymphocyte Stimulator surface (and blank control) using the following program:

MAIN			
FLOWCELL 1,2,3,4			
APROG	genab	r1d1	ab1
APROG	genab	r1d2	ab2
APROG	genab	r1d3	ab3

-continued

```

APROG genab rld4 ab4
APROG genab rld5 ab5
APROG genab rld6 ab6
APPEND CONTINUE
END
DEFINE APROG genab
PARAM %Abpos %Abld
FLOW 20
KINJECT %Abpos 200 80
INJECT rlc6 10lguanidine hydrochloride regeneration step
EXTRACT.FAN
END

```

Bound scFvs were removed by injecting 10 μ l 4M GuHCl in HBS over the surface between scFv samples.

The binding curves for individual scFvs were analyzed using the BIAevaluation software to determine antibody off-rates. Kinetic analysis for a typical scFv antibody, I003C02, is shown in FIG. 5. I003C02 has a $K_{off}=6 \times 10^{-3} \text{ s}^{-1}$.

Example 7

Inhibition in an In Vitro Receptor Binding Assay by scFv Antibodies

The 48 scFvs listed in Table 3 were purified and assessed for their ability to inhibit B Lymphocyte Stimulator binding to its receptor on IM9 cells.

Purification of scFv

To determine the inhibitory potency of anti-B Lymphocyte Stimulator scFv, scFv's were first prepared by IMAC. 2TYAG (5 ml) was inoculated with a single colony and grown overnight at 30° C., shaking. This overnight culture was then used to inoculate 500 ml of 2TY containing 100 μ g/ml ampicillin and 0.1% Glucose, and grown at 30° C., shaking, until an A_{600} of 1.0 was attained. IPTG was added to 1 mM and the culture was grown for a further 3.5 hours at 30° C.

Cells were harvested by centrifugation at 5,000 rpm, and resuspended in 10 ml of TES. A further 15 ml of a 1:5 dilution (in water) of TES was added, and the cell suspension incubated on a turning wheel at 4° C. for 30 minutes. This causes osmotic shock and yields a periplasmic extract containing the scFv. Residual cells and debris were pelleted by centrifugation at 9,000 rpm for 20 minutes at 4° C. The supernatant was transferred to a new tube, and 50 μ l of 1 M MgCl_2 added. Two ml of a Ni-NTA agarose (Qiagen), pre-washed with buffer (50 mM sodium phosphate, pH 8, 300 mM NaCl) together with a protease inhibitor tablet (Boehringer Mannheim) were then added to the periplasmic extract. The preparation was incubated, rotating, overnight at 4° C. The Ni-NTA was pelleted by centrifugation at 2,000 rpm for 5 minutes, and the supernatant was aspirated. The agarose beads were washed 3 times with 50 ml wash buffer, centrifuging to collect the agarose in between each wash. Ten ml of wash buffer was added after the final wash, and the slurry was loaded on to a polyprep column (BioRad). Two ml elution buffer (50 mM NaPi (sodium phosphate), pH 8, 300 mM NaCl, 250 mM imidazole) was added to the drained agarose, and the eluate was collected. IMAC purified scFv was buffer exchanged in to PBS by use of a Nap 5 column (Pharmacia) according to the manufacturer's instructions. The A2S was read and the protein concentration determined using a molar extinction coefficient of 1 mg/ml protein= A_{280} 1.4. Purified scFv was stored in 500 μ l aliquots at -70° C.

Receptor Binding Inhibition Assay

Flat-bottomed 96-well plates (Costar) were coated with 100 μ l per well of a 1:10 dilution of poly-L-lysine (Sigma) in PBS for 1 hour at room temperature. The plates were then washed twice with water, allowed to air-dry and placed at 4° C. overnight. One hundred μ l of IM9 cells (at 10^6 /ml in RPMI-1640) were then added to each well. Plates were then centrifuged at 3200 rpm for 5 mins to pellet the cells. The media was carefully aspirated and 200 μ l of MPBS added to each well. The plates were then left to block for 1 hour at room temperature.

To a separate 96-well plate, titrate test scFvs in MPBS, in triplicate, over a concentration range from 10 μ g/ml down to 0.001 μ g/ml were added. The final volume of test scFv in each well was 55 μ l. Competition with unlabelled B Lymphocyte Stimulator was also included in every assay as a control. Unlabelled B Lymphocyte Stimulator, in MPBS, was typically titrated in triplicate, over a concentration range from 1 μ g/ml down to 0.001 μ g/ml. 10 μ l of biotinylated-B Lymphocyte Stimulator (at 162.5 ng/ml) in MPBS was added to each well to give a final concentration of 25 ng/ml. Plates were then incubated at room temperature for 30 minutes.

The IM9 coated plates was washed twice in PBS, tapped dry and immediately 50 μ l of the scFv/biotinylated-B Lymphocyte Stimulator mix was added and incubated at room temperature for 1 hour. Plates were washed three times in PBST and three times in PBS, tapped dry and 50 μ l per well added of streptavidin-Delfia (Wallac) at 1:1000 dilution in the Manufacturer's assay buffer. The plates were then incubated at room temperature for 1 hour and washed six times in Delfia wash solution (Wallac). After tapping the plates dry, 100 μ l per well of Delfia enhancement solution (Wallac) was added. The plates were gently tapped to encourage micelle formation, incubated at room temperature for 10 minutes, and fluorescence read on a Wallac 1420 workstation at 6520 nM.

Typical titration curves for two scFv antibodies, I007F11 and I050A07, are shown in FIG. 6. Unlabelled B Lymphocyte Stimulator competed for binding to its receptor with an IC_{50} value of 0.8 nM. The IC_{50} values for I007F11 and I050A07 are 7.9 nM and 17.1 nM, respectively. The assay was performed in triplicate and standard error bars are shown. The 9 scFvs that demonstrated the greatest inhibition as scFv are listed in Table 4. This data also confirms that these 9 scFvs recognize the soluble form of B Lymphocyte Stimulator.

TABLE 4

9 ScFvs that demonstrated greatest potency in B Lymphocyte Stimulator Receptor Binding Inhibition Assay

ScFv Antibody

I017D10
I022D01
I008A11
I006D08
I031F02
I050A12
I050B11
I051C04
I003F12S

Antibodies Recognizing a Soluble form of B Lymphocyte Stimulator

A library of phage was screened in an assay to identify those phage displaying scFvs that immunospecifically bind to the soluble but not the membrane-bound forms of B Lymphocyte Stimulator.

A phage library was screened for the ability to bind to biotinylated B Lymphocyte Stimulator. The phage were exposed to biotinylated B Lymphocyte Stimulator, allowed an interval of time to bind the biotinylated B Lymphocyte Stimulator. Phage binding bio-B Lymphocyte Stimulator were then isolated by capture on streptavidin coated magnetic beads.

The phage identified in the screen above (capture of Bio-B Lymphocyte Stimulator from solution) were then screened by ELISA for their ability to bind immobilized B Lymphocyte Stimulator. The scFv expressed by phage that bound immobilized B Lymphocyte Stimulator were then cloned and sequenced. Again, several sequences were identified multiple times, thus a panel (panel 2) consisting of an example of each phage expressing a unique scFv was then characterized further.

The derived amino acid sequences of these scFvs are shown in Table 1 above. The individual VH and VL segments of the scFvs were aligned to the known human germline sequences in V-BASE (Tomlinson et al, which can accessed on the United Kingdom Medical Research Council (MRC) Centre for Protein Engineering website) and the closest germline identified.

Example 9

Specificity For Soluble B Lymphocyte Stimulator

The scFvs were isolated from a library of phage based on their ability to bind a soluble form of B Lymphocyte Stimulator. Briefly, phage were preincubated with biotinylated B Lymphocyte Stimulator in solution. Phage that bound to this biotinylated B Lymphocyte Stimulator were then isolated using streptavidin coated magnetic beads.

The specificity of each of the unique scFvs for B Lymphocyte Stimulator and for the membrane-bound form of B Lymphocyte Stimulator, was determined by phage ELISA. B Lymphocyte Stimulator was immobilised onto plastic as a purified soluble form of the protein or as a membrane-bound form present on plasma membrane preparations from the human macrophage-like cell line, U937. Maintenance of U937 cells and plasma membrane preparations were performed as detailed in Example 2.

Phage ELISA

To determine the specificity of each of the scFvs, a phage ELISA was performed for each antibody against human B Lymphocyte Stimulator, U937 plasma membranes, TNF α , BSA and an uncoated well. Antigen coating conditions were as described in Example 2, apart from human B Lymphocyte Stimulator. B Lymphocyte Stimulator was first biotinylated (as described in Example 3) and coated at 1 μ g/ml onto streptavidin coated plates (Reacti-Bind, Pierce) for 30 mins at room temperature. The plates were then washed, blocked and the phage ELISA performed as detailed in Example 2.

The results for 3 clones (I074B12, I075F12 and I075A02) that bind the soluble but not the membrane-bound form of B Lymphocyte Stimulator are shown in FIG. 7. As a control, a

phage antibody that recognizes TNF α , is also shown in FIG. 7. There is a small non-specific background signal on the U937 plasma membranes that is evident with both the anti-B Lymphocyte Stimulator scFvs as well as the anti-TNF α control. All 3 anti-B Lymphocyte Stimulator scFvs recognize B Lymphocyte Stimulator but not U937 plasma membranes, TNF α , BSA or an uncoated well (PBS only). This indicates that the scFvs do not bind the membrane-bound form of B Lymphocyte Stimulator. Further, The fact that these scFvs were isolated on the basis of their ability to bind soluble biotinylated B Lymphocyte Stimulator indicates that they bind the soluble form of B Lymphocyte Stimulator. Further confirmation of these scFvs' specificity for B Lymphocyte Stimulator is provided in Example 10.

Example 10

Inhibition in an In Vitro Receptor Binding Assay by Phage scFvs

All of the unique phage scFvs from panel 2 were assessed for their ability to inhibit B Lymphocyte Stimulator binding to its cognate receptor on IM9 cells. The biotinylation of B Lymphocyte Stimulator, maintenance of IM9 cells and receptor binding inhibition assay were performed as described in Example 3.

Results for two phage scFvs, I0025B09 and I026C04 are shown in FIG. 8. Maximal binding of biotinylated B Lymphocyte Stimulator to its receptor (bio-B Lymphocyte Stimulator only), the background signal in the absence of biotinylated B Lymphocyte Stimulator (no bio-B Lymphocyte Stimulator), and results with an irrelevant (i.e. does not recognize B Lymphocyte Stimulator) phage antibody are also shown. Both phage scFvs inhibited biotinylated B Lymphocyte Stimulator binding to its receptor on IM9 cells. 33 of the unique scFvs from panel 2 were identified for further study. These 33 scFvs demonstrated the greatest inhibition as phage particles in this assay and are listed in

TABLE 5

Identification of 33 phage scFvs to free B Lymphocyte Stimulator that demonstrate the most significant inhibition of biotinylated-B Lymphocyte Stimulator binding to its receptor

Antibody	Antibody	Antibody	Antibody
I026C04	I074B12	I073F04	I065D04
I003C06	I075A02	I078D08	I068C08
I025B09	I068B08	I078D02	I068F03
I027B12	I068B04	I075G01	I069B07
I025B06	I068C06	I071B03	
I030A10	I075F12	I072B09	
I002A01R	I065D08	I078H08	
I002A01K	I065F08	I064C04	
I026C04R	I067B10	I064C07	
I026C04K	I067F05		

Example 11

Specificity of Anti-B Lymphocyte Stimulator scFvs

The specificity of the 33 scFvs (listed in Table 5) for immobilized human and murine B Lymphocyte Stimulator was determined using phage ELISA.

Phage ELISA

To determine the specificity of the 33 scFvs, a phage ELISA was performed as described in Example 4 against

human and mouse B Lymphocyte Stimulator, and a panel of related human antigens: TRAIL, LIGHT, TNF α , TNF β , and an uncoated well (PBS only).

Typical results for two scFvs, I067F05 and I078D02 are shown in FIG. 9. A control antibody that specifically recognizes TNF α is also shown. Both anti-B Lymphocyte Stimulator scFvs specifically recognize immobilized human and mouse B Lymphocyte Stimulator but not any other antigen tested.

All 33 scFvs are specific for human B Lymphocyte Stimulator. $^{1/33}$ cross-react with mouse B Lymphocyte Stimulator but not with any other unrelated or related antigen tested.

Example 12

scFv Off-Rate Determinations

Off-rate determinations, preparation of a low density B Lymphocyte Stimulator surface and kinetic measurements were as detailed in Example 6.

The binding curves for individual scFvs were analysed using the BIAevaluation software to determine antibody off-rates. Kinetic analysis for a typical scFv antibody, I002A01, is shown in FIG. 10. I002A01 has a $K_{off}=9 \times 10^{-4} \text{ s}^{-1}$.

Example 13

Inhibition in an In Vitro Receptor Binding Assay by scFv Antibodies

The 33 scFvs identified in Table 5 were prepared as purified scFvs and assessed for their ability to inhibit B Lymphocyte Stimulator binding to its receptor on IM9 cells. The scFvs were purified and analysed in the receptor binding inhibition assay as described in Example 6.1.8.

Typical titration curves for two scFvs, I0068C06 and I074B12, are shown in FIG. 11. Unlabelled B Lymphocyte Stimulator competed for binding to its receptor with an inhibitory constant 50 (IC_{50}) value of 0.66 nM. The IC_{50} values for I0068C06 and I074B12 are 61 nM and 13 nM, respectively. The assay was performed in triplicate and standard error bars are shown. The 7 scFvs that demonstrated the greatest inhibition as scFv are listed in Table 6.

TABLE 6

Identification of 7 scFvs to free B Lymphocyte Stimulator that demonstrate the most significant inhibition of biotinylated-B Lymphocyte Stimulator binding to its receptor as purified scFv's.	
Antibody	
I002A01-R	
I002A01-K	
I026C04-R	
I026C04-K	
I068C06	
I075F12	
I067B10	

Example 14

ScFvs Recognizing Membrane-Bound B Lymphocyte Stimulator

A library of phage was screened in an assay to identify those phage displaying scFvs that immunospecifically bind to the membrane-bound but not the soluble form of B Lymphocyte Stimulator.

As a starting point, a library of phage expressing scFv antibodies were panned on immobilized HIS-tagged B Lymphocyte Stimulator. Phage isolated by panning were then screened for the ability to bind to HIS-tagged B Lymphocyte Stimulator. HS-tagged B Lymphocyte Stimulator was obtained by expressing amino acids 71-285 of SEQ ID NO:3228 using the pQE9 vector (Qiagen Inc., Valencia, Calif.) in *E. coli* and purifying the expressed protein. This phage clones identified by this screen were then sequenced. After sequencing, A panel (panel 3) of phage each expressing a unique scFv that bound HIS-tagged B Lymphocyte Stimulator was generated and further characterized.

The derived amino acid sequences of the unique scFvs from panel 3 are shown in Table 1 above. The individual V_H and V_L segments of the scFvs were aligned to the known human germline sequences in V-BASE (Tomlinson et al, which can accessed on the United Kingdom Medical Research Council (MRC) Centre for Protein Engineering website) and the closest germline identified.

Example 15

Recognition of Membrane-Bound B Lymphocyte Stimulator

The specificity of each of the unique scFvs for both the membrane-bound form of B Lymphocyte Stimulator as well as for the soluble form of B Lymphocyte Stimulator, was determined by phage ELISA. B Lymphocyte Stimulator was immobilised onto plastic either directly as a purified soluble form of the protein or biotinylated and coated on a streptavidin plate as in Example 9. Binding to HIS-tagged B Lymphocyte Stimulator was used as a primary screen for scFv's that would bind the membrane-bound form of B Lymphocyte Stimulator (see below). The membrane-bound form of B Lymphocyte Stimulator was presented as plasma membranes preparations from the human macrophage-like cell line, U937 or the murine cell line P388.

Mouse monoclonal antibodies have been raised against His-tagged B Lymphocyte Stimulator according to standard procedures. Characterization of these mouse monoclonal antibodies revealed that they specifically recognized both His-tagged B Lymphocyte Stimulator and the membrane-bound form of B Lymphocyte Stimulator on U937 cells, but not soluble B Lymphocyte Stimulator. Therefore, specific recognition of His-tagged B Lymphocyte Stimulator was used as supporting evidence for the recognition of the membrane-bound form of B Lymphocyte Stimulator by phage and scFv antibodies.

Phage ELISA

To determine the specificity of each of the scFvs, a phage ELISA was performed for each antibody against His-tagged human B Lymphocyte Stimulator, U937 plasma membranes, TNF α , BSA and an uncoated well. Antigen coating conditions were as described in 2. apart from human B Lymphocyte Stimulator. B Lymphocyte Stimulator was first biotinylated (as described in Example 3) and coated at 1 $\mu\text{g/ml}$ onto streptavidin coated plates (Reacti-Bind, Pierce) for 30 mins at room temperature. The plates were then washed, blocked and the phage ELISA performed as detailed in Example 2.

The results for 3 clones, I079C01, I081C10 and I082A02, and a control phage antibody that recognizes TNF α , are shown in FIG. 12. AU 3 scFvs recognize U937 plasma membranes (U937) and His-tagged B Lymphocyte Stimulator (HIS-B Lymphocyte Stimulator) but not, biotinylated B Lymphocyte Stimulator (bio-B Lymphocyte Stimulator) or an

uncoated well (PBS). This indicates that the scFvs recognize the membrane-bound form of B Lymphocyte Stimulator.

Example 16

Specificity for Membrane-Bound B Lymphocyte Stimulator

The specificity of the scFvs for only the membrane-bound form of B Lymphocyte Stimulator, and not for the soluble form, was confirmed using a competition ELISA. This assay assesses the ability of test phage scFvs to bind to the membrane-bound form of B Lymphocyte Stimulator on U937 plasma membranes in the presence of different forms of competing B Lymphocyte Stimulator. Competing B Lymphocyte Stimulator was either the His-tagged form of B Lymphocyte Stimulator or soluble B Lymphocyte Stimulator. ScFvs specific for the membrane-bound B Lymphocyte Stimulator would be expected to be competed out by pre-incubation with His-tagged B Lymphocyte Stimulator but not by pre-incubation with soluble B Lymphocyte Stimulator.

Maintenance of U937 cells and plasma membrane preparations were performed as detailed in Example 2. Competition ELISA

U937 plasma membranes (50 μ l per well) were coated at 10 μ g/ml in PBS onto Falcon 96-well plates overnight at 4° C.

Individual *E. coli* colonies containing a phagemid representing one of the unique scFvs from the panel 3 were inoculated into 50 ml tubes (Falcon) containing 5 ml 2TYAG medium. Tubes were incubated at 37° C. for 4 hours, shaking. M13KO7 helper phage was added to each tube to an MOI of 10 and the tubes were incubated for a further 1 hour at 37° C. The tubes were centrifuged in a benchtop centrifuge at 3500 rpm for 10 minutes. The supernatant was removed and cell pellets were resuspended in 5 ml 2TYAG and incubated at 30° C. overnight, shaking. The next day, tubes were centrifuged at 3500 rpm for 10 min and the phage-containing supernatant carefully transferred into a fresh tube.

For each test phage antibody, 3 aliquots of 20 μ l 18% marvel/6xPBS were transferred into separate wells of a 96-well plate. The first aliquot was supplemented with His-tagged B Lymphocyte Stimulator to a final concentration of 60 μ g/ml. The second aliquot was supplemented with soluble B Lymphocyte Stimulator to a final concentration of 60 μ g/ml. The third aliquot was not supplemented with any competing antigen. One hundred μ l of phage supernatant was then added to each aliquot and left to block at room temperature for 1 hour.

The antigen-coated plates were washed once with PBS before the addition of 200 μ l/well 3% marvel/PBS. These plates were left to block at 37° C. for 1 hour and were then washed once with PBS. Duplicate samples of 50 μ l pre-blocked phage (above) were added to the antigen-coated plates and left at room temperature for 1 hour. Plates were washed 3x with PBS/0.1% Tween 20, then 3x with PBS. Fifty μ l/well mouse anti-M13 HRP (Pharmacia) at 1/5000 in 3% Marvel/PBS was added and left for 1 hour at room temperature. Plates were washed 3 times with PBS/0.1% Tween 20, then 3 times with PBS. Fifty μ l/well HRP-labelled anti-mouse Envision polymer (DAKO) at 1/50 in 3% marvel/PBS was added and left for 1 hour at RT. Plates were washed 3 times with PBS/0.1% Tween 20, then 3 times with PBS. Next, 50 μ l/well of TMB (Sigma) was added and plates left to develop for 30 to 60 minutes. When sufficient color has developed, 25 μ l/well 0.5M H₂SO₄ was added to stop the reaction. The plates were read at 450 nm on a microtiter plate reader (Bio-Rad 3550).

The results for 3 clones, I079B04, I079F08 and I080B01, and a control phage antibody that recognizes TNF α , are shown in FIG. 13. All 3 scFvs recognize U937 plasma membranes (U937). This binding is competed out to background levels (i.e. comparable to the signal observed with the anti-TNF α phage antibody) in the presence of His-tagged B Lymphocyte Stimulator (HIS-B Lymphocyte Stimulator) but not biotinylated B Lymphocyte Stimulator (bio-B Lymphocyte Stimulator). This confirms that the scFvs specifically recognize the membrane-bound form but not the soluble form of B Lymphocyte Stimulator.

Example 17

High Throughput BIAcore Screen to Identify High Affinity scFvs

This is a 96-well screen where the test samples (scFvs) are derived from 1 ml periplasmic extracts of individual antibody expressing clones. Potentially higher affinity scFvs are then identified principally as those giving a large number of total RU's bound to a HIS-B Lymphocyte Stimulator surface in BIAcore. This method of ranking does assume approximately equal yields of scFv from each clone. Since this is not always the case, some scFvs may also be identified that simply express high levels of scFv. These can be discriminated from those of higher affinity by further characterization of the scFvs (see Example 18).

Preparation of ScFv from 1 ml *E. coli* Cultures

Individual *E. coli* colonies containing a phagemid representing one of the unique scFvs from panel 3 were inoculated into 96-well plates containing 100 μ l 2TYAG medium per well. Eight wells on each plate were reserved for positive and negative control samples. The plate was grown overnight at 30° C. with shaking at 120 rpm.

Next day, 1 ml of 2TYAG +345 mM sucrose was added to each well of an autoclaved 96 deep well plate (Beckman). Twenty μ l of each overnight culture was resuspended and transferred to the appropriate well of the deep well plate. The plate was grown for approximately 3.5 hours at 30° C. with shaking at 250 rpm (or until the OD₆₀₀=0.6). Fifty μ l of 1M IPTG was added to 5 ml 2TY and 10 μ l of this was added to each well. The plate was grown overnight at 30° C. with shaking at 250 rpm.

Plates were kept at 4° C. for the remainder of the procedure. The overnight plate (above) was centrifuged at 3500 rpm for 10 minutes at 4° C. to pellet the cells. The supernatant was decanted and each pellet resuspended in 100 μ l TES (0.2M Tris HCl pH8.0, 0.5 mM EDTA, 0.5M sucrose) and transferred to a fresh 96 well plate. This plate was incubated on ice for 30 minutes and then centrifuged for 10 minutes at 3500 rpm at 4° C. to pellet the cell debris. During centrifugation, 15 μ l of freshly made protease inhibitors cocktail (Roche, 1 tablet dissolved in 1.5 ml water) was added to each well of a fresh 96 well plate. Supernatants from the centrifuged plate were then transferred to the plate containing the protease inhibitors. The plate was centrifuged at 3500 rpm for 10 minutes at 4° C. and the supernatant was transferred to a further 96-well plate. This step was repeated at least once more or until there was no sign of any cell debris following centrifugation. Finally, the plate was covered in foil to prevent evaporation of samples during the BIAcore run.

Generation of a High Density HIS-B Lymphocyte Stimulator Surface

All BIAcore analysis was performed on BIAcore 2000 machines, using the BIAcore 2000 control software and

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evaluated using the BIAevaluation 3.0 software. A high density His-tagged B Lymphocyte Stimulator surface (>1000 RU HIS-B Lymphocyte Stimulator coupled) was prepared in flow cell 2 by amine coupling to a CM5 chip. A new CM5 chip was inserted into the BIAcore and a sensorgram started over flow cell 2 with HBS buffer at a flow rate of 5 μ l/min. The NHS and EDC solution were mixed 1:1 before injecting 30 μ l over the CM5 surface. Fifty μ l HIS-B Lymphocyte Stimulator (at 10 μ g/ml in Sodium acetate buffer, pH4) was injected and allowed to couple to the surface. Thirty μ l of ethanolamine-HCl solution was then injected to block free NHS esters. Prior to using the chip, 10 μ l of 4M Guanidine hydrochloride in HBS was injected over the surface to strip the surface of non-covalently bound B Lymphocyte Stimulator. A blank surface (no HIS-B Lymphocyte Stimulator) was also prepared over flow cell 1 so that non-specific binding effects can be subtracted from the HIS-B Lymphocyte Stimulator binding curves.

Typically, a 5000 RU His-tagged B Lymphocyte Stimulator surface was generated in this way and used for 96-well analysis of scFvs isolated from the periplasm of *E. coli*.

BIAcore Analysis

The 96-well plate containing periplasmic scFvs was secured inside the BIAcore. Two ml of 4M Guanidine hydrochloride in HBS was placed in a rack inside the BIAcore for regeneration of the HIS-B Lymphocyte Stimulator surface between samples. The sensorgram was run over flow cells 1 and 2 at a flow rate of 20 μ l/minute. The following method was run:

```

MAIN
FLOWCELL 1,2,3,4
LOOP cycle STEP
APROG inj %pos
ENDLOOP
APPEND CONTINUE
END
DEFINE LOOP cycle
LPARAM %pos
r1a1
r1b1
r1c1
r1d1
r1e1
r1f1 etc (all wells listed until r1h12)
END
DEFINE APROG inj
PARAM %pos
FLOW 20
KINJECT %pos 35 30 1scfv injection
QUICKINJECT r2f3 10 1regeneration
EXTRACLEAN
END

```

When the run had finished, the sensorgram data for flow cell 1 was subtracted from the data for flow cell 2 for each sample using the BIAevaluation software. The clones were compared with one another principally by overall RU change as the scFv dissociates from the surface. In addition a few scFvs were identified as having potentially slower off-rates. An example of the dissociation section of a typical sensor gun for 8 scFvs is shown in FIG. 14. An anti-TNF α antibody that does not recognize B Lymphocyte Stimulator was included as a control. Of the 8 scFvs exemplified, I079F06 was identified for further study due to the relatively high numbers of RU's bound to the surface.

ScFvs were identified principally if they demonstrated a RU change of over 1200, a few were also identified as having

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potentially slower than typical off-rates. A total of 28 clones were chosen on these criteria and are listed in Table 7.

TABLE 7

Identification of 28 antibodies to membrane-bound B Lymphocyte Stimulator that demonstrate the most significant RU changes by BIAcore

Antibody	Antibody
I079C01	I084C04
I082H08	I080E05
I079E02	I083B12
I079B05	I082G01
I079F06	I082G02
I079F08	I082C03
I079F11	I082A05
I079B12	I082D07
I080B01	I082B08
I080G09	I084A01
I099D03	I084B02
I080D03	I080A08
I080A03	I084C11
I083G03	
I080G07	

Example 18

scFv Affinity Determinations

The affinity (K_D) of the 28 scFvs was determined using the BIAcore.

Low Density HIS-B Lymphocyte Stimulator Surface for Kinetic Studies

500RU surfaces were used for kinetic studies of purified scFv binding to HIS-B Lymphocyte Stimulator. The method to prepare these surfaces was identical to the method described in Example 17, only smaller volumes of HIS-B Lymphocyte Stimulator were injected.

Measurement of scFv Binding Kinetics

The chip containing the low density HIS-B Lymphocyte Stimulator surface was inserted into the BIAcore. A dilution series for each of the 28 purified scFvs (prepared as in Example 6) were diluted in HBS (typically starting with 50 μ g/ml scFv and double diluting down to 1.5 μ g/ml). The dilution series was then injected sequentially over the blank control (flow cell 1) and low density HIS-B Lymphocyte Stimulator surface (flow cell 2) using the following program:

```

MAIN
FLOWCELL 1,2,3,4
APROG genab r1d1 ab1
APROG genab r1d2 ab2
APROG genab r1d3 ab3
APROG genab r1d4 ab4
APROG genab r1d5 ab5
APROG genab r1d6 ab6
APPEND CONTINUE
END
DEFINE APROG genab
PARAM %Abpos %Abld
FLOW 20
KINJECT %Abpos 200 80
INJECT r2f3 10
EXTRACLEAN
END

```

Bound scFv were removed by injecting 10 μ l of 4M Guanidine hydrochloride in HBS (location r2f3 in the above pro-

gram) over the surface between samples. Binding curves for individual scFv were analysed using the BIAevaluation software to determine antibody on- and off-rates.

A typical example of the binding curves generated for the scFv antibody I082C03 is shown in FIG. 15. The off-rate for this clone was calculated as $2 \times 10^{-3} \text{ s}^{-1}$. The affinity of I082C03 was calculated as 20 nM, assuming 100% activity of the scFv. The 5 scFvs with the highest affinities as scFvs are given in Table 8.

TABLE 8

Identification of 5 antibodies to membrane-bound B Lymphocyte Stimulator that have the highest affinities as scFvs	
Antibody	Affinity (K_D)
I079F11	5 nM
I079E02	10 nM
I082G02	6 nM
I082H08	1 nM
I099D03	4 nM

Example 19

Recognition of Mouse Membrane-Bound B Lymphocyte Stimulator

The ability of the 5 scFvs listed in Table 8 to also recognize murine membrane-bound B Lymphocyte Stimulator was determined using a competition ELISA. This assay assesses the ability of test phage scFvs to bind to the membrane-bound form of B Lymphocyte Stimulator on the murine cell line, P388, plasma membranes in the presence of different forms of competing human B Lymphocyte Stimulator. Competing B Lymphocyte Stimulator was either presented as the His-tagged form of B Lymphocyte Stimulator, or soluble B Lymphocyte Stimulator. ScFvs that recognize mouse membrane-bound B Lymphocyte Stimulator would give an ELISA signal on the P388 plasma membranes that is competed out by pre-incubation with HIS-tagged B Lymphocyte Stimulator but not by pre-incubation with soluble B Lymphocyte Stimulator.

Maintenance of P388.D1 Cells and Preparation of Plasma Membranes

P388.D1 cells are a mouse monocyte-macrophage like cell line. They were cultured in L-15 medium supplemented with 2 mM L-glutamine, 10% CS, 10U penicillin, 100 g/ml streptomycin (all reagents from Sigma). Cells were split 1:4 every 3-4 days to maintain a cell density of $2-8 \times 10^5$ per ml. A fresh aliquot of cells was thawed from liquid nitrogen every 6 weeks. Plasma membrane fractions were prepared as described in Example 2.

Competition ELISA

P388 plasma membranes (50 μ l per well) were coated at 10 g/ml in PBS onto Falcon 96-well plates overnight at 4°C. The method is otherwise essentially as described Example 16.

The results for 3 clones, I079E02, I082H08 and I099D03 are shown in FIG. 16. All 3 scFvs recognize P388 plasma membranes. This binding is competed out in the presence of HIS-tagged B Lymphocyte Stimulator (HIS-B Lymphocyte Stimulator) but not in the presence of biotinylated B Lymphocyte Stimulator (bio-B Lymphocyte Stimulator). This confirms that these scFvs also recognize the membrane-bound form but not the soluble form of mouse B Lymphocyte Stimulator.

Example 20

Conversion of scFvs to IgG1 Format

The VH domain and the VL domains of scFvs that we wished to convert into IgG molecules were cloned into vectors containing the nucleotide sequences of the appropriate heavy (human IgG1) or light chain (human kappa or human lambda) constant regions such that a complete heavy or light chain molecule could be expressed from these vectors when transfected into an appropriate host cell. Further, when cloned heavy and light chains are both expressed in one cell line (from either one or two vectors), they can assemble into a complete functional antibody molecule that is secreted into the cell culture medium. Methods for converting scFvs into conventional antibody molecules are well known within the art.

Generation of NS0 Cell Lines Expressing anti-B Lymphocyte Stimulator Antibodies (IgG1)

Plasmids containing the heavy and light chains were separately linearized using the Pvu I restriction enzyme. The linearized DNAs were purified by phenol-chloroform extraction followed by ethanol precipitation and then resuspended in H₂O. NS0 cells (10^7) from a growing culture were electroporated (0.25 kV and 975 μ F) in PBS with 12.5 μ g linearized heavy chain plasmid DNA and 37.5 μ g linearized light chain DNA. The cells were washed in 20 ml non-selective medium (10% FCS in DMEM supplemented with 6 mM glutamine, amino acids and penicillin/streptomycin) and then transferred in 12.5 ml medium into a T75cm² flask and incubated overnight at 37°C, 5% CO₂/air. The day after transfection the cells were resuspended in selective medium containing 1 mg/ml geneticin and dispensed into 5x96-well plates at 200 μ l/well. After 18 days at 37°C (5% CO₂/air) the colony supernatants were screened by an ELISA that detects assembled human IgG in order to identify colonies expressing IgG. Approximately twenty positive colonies were expanded and adapted to growth in serum-free, selective medium. Duplicate T25cm² flasks were set up. Cells from one flask were frozen down as a stock and cells in the second flask were grown to saturation. The productivity of the saturated cultures was assessed by ELISA. The highest producing cell lines were then selected for large-scale antibody production.

The above procedure is exemplified for the I006D08 anti-B Lymphocyte Stimulator antibody constructs. Following electroporation and selection of NS0 cells, supernatants from ninety-three wells each containing a single colony were screened by ELISA to detect assembled IgG1 antibody. Twenty-seven of the supernatants were identified as containing IgG. The colonies from 24 of the positive wells were transferred to 1 ml selective medium in a 24-well plate and allowed to grow for 2 days. The 1 ml cultures of cells were then added to 4 ml selective medium containing reduced serum (0.5% FCS) in a T25cm² flask. When the cultures reached confluency 1 ml cells were diluted in 4 ml selective, serum-free medium in a T25cm² flask. At confluency this subculture regime was repeated again. Finally 1 ml cells from the culture containing 0.1% FCS was diluted with 9 ml serum-free, selective medium and divided into 2xT25cm² to form the saturated and stock cultures. The stock cultures were frozen down and stored in liquid nitrogen once the cultures were confluent. The saturation culture was grown until the viability of the culture was <10%. Twenty-three out of the 24 colonies originally expanded were successfully adapted to growth in serum-free medium. The productivity of these serum-free adapted cell lines ranged from 0.3 to 17 μ g/ml by

ELISA quantification of the saturated, 5 ml serum-free cultures. The I006D08-32 cell line produced 17 µg/ml.

Large-Scale IgG Production

The highest-producing cell lines were revived from frozen stocks and then expanded to 400 ml in selective, serum-free medium in 2 liter roller bottles. The cells were grown at 37° C. and rolled at 4 rpm with the headspace being re-equilibrated with 5% CO₂/air every 2-3 days. Finally the culture was expanded to a 4 liter volume by the addition of serum-free medium without selection (400 ml per 2 liter roller bottle). The cultures were then grown to saturation.

This procedure is exemplified by the production of I006D08 antibody from the I006D08-32 cell line. The frozen stock of I006D08-32 was revived into a T25 cm² containing 5 ml serum-free medium containing 1 mg/ml geneticin and grown at 37° C. in 5% CO₂/air incubator. After two days growth the culture was diluted with 7.5 ml fresh medium and transferred to a T75cm² flask. After a further three days in the incubator the cells were transferred to 130 ml selective medium and transferred to a 2 liter roller bottle. After three days growth the cells were diluted with 500 ml selective medium and split into 2x2 liter roller bottles. After another 2 days 100 ml fresh selective medium was added to each roller. Finally the next day the culture was expanded to a total volume of 4 liters with non-selective medium and divided into 10x2 liter roller bottles. After three days the medium was supplemented with 6 mM glutamine. The cells were grown for 17 days from the final subculture into a 4 liter volume. The cells grew up to 3x10⁶ cells/ml before viability declined to <0.2x10⁶ cells/ml. At this low viability the culture supernatants were harvested. ELISA analysis indicated that the culture supernatant contained 33 µg/ml IgG. Hence, the 4 liter culture contained 132 mg IgG.

IgG Purification

The purification of the IgG from the fermentation broth is performed using a combination of conventional techniques commonly used for antibody production. Typically the culture harvest is clarified to remove cells and cellular debris prior to starting the purification scheme. This would normally be achieved using either centrifugation or filtration of the harvest. Following clarification, the antibody would typically be captured and significantly purified using affinity chromatography on Protein A Sepharose. The antibody is bound to Protein A Sepharose at basic pH and, following washing of the matrix, is eluted by a reduction of the pH. Further purification of the antibody is then achieved by gel filtration. As well as removing components with different molecular weights from the antibody this step can also be used to buffer exchange into the desired final formulation buffer.

Purification of I006D08 IgG1

The harvest was clarified by sequential filtration through 0.5 µm and 0.22 µm filters. Clarified harvest was then applied to a column of recombinant Protein A Sepharose equilibrated at pH 8.0 and washed with the equilibration buffer. I006D08 antibody was eluted from the Protein A Sepharose by application of a buffer at pH 3.5. The collected antibody containing eluate was then neutralized to pH 7.4 by the addition of pH 8.0 buffer. The neutralized eluate was concentrated by ultrafiltration using a 30 KDa cut off membrane. Concentrated material was then purified by Sephacryl S300HR gel filtration using phosphate buffered saline as the mobile phase. The final monomeric IgG1 fraction from the gel filtration column was then concentrated to the desired formulation concentration by ultrafiltration using a 30 KDa cut off membrane. The final product was filtered through a 0.22 µm filter.

Example 21

Antibody Neutralization of Murine Splenocyte Proliferation as Measured by 3HdT Incorporation

To determine if an antibody inhibited B Lymphocyte Stimulator mediated B cell proliferation, a splenocyte proliferation assay was performed. Briefly, murine splenocytes were isolated by flushing spleen with complete medium using a 25 g needle and 10 ml of complete medium (RPMI 1640 with 10% FBS containing 100U/ml penicillin, 100 µg/ml streptomycin, 4 mM glutamine, 5x10⁻⁵M β-mercaptoethanol). The cells were passed through a 100 micron nylon filter to remove cell clumps. The cell suspension was then ficolled at 400xg for 25 minutes at room temperature (one 15 ml conical tube/spleen; 3 ml ficol, 10 ml cell suspension/spleen; Ficoll 1083 from Sigma). The recovered cells were washed 3 times in complete medium and counted. Recovered cells were then diluted to a concentration of 3x10⁶/ml in complete medium containing a 3x concentration of SAC (3x=1:33,333 dilution of stock) (*Staph. aureus* Cowan strain; Calbiochem).

For each antibody, 50 microliters of antibody dilutions at 30 µg/ml, 3.0 µg/ml and 0.3 µg/ml concentrations were aliquotted into individual wells of a 96 well plate in triplicate. Suitable positive controls, such as, for example monoclonal antibody 15C10, were also used. Medium containing no antibody (and human isotype controls (purchased commercially) when necessary) were used as negative controls.

B Lymphocyte Stimulator protein was diluted in complete medium to concentrations of 300 ng/ml, 90 ng/ml and 30 ng/ml. 50 microliters of each of the B Lymphocyte Stimulator dilutions were then added to the antibody dilution series in the plates. The plate containing the antibody and B Lymphocyte Stimulator dilutions are then incubated for 30 minutes at 37° C., 5% CO₂, after which 50 microliters of the splenocyte cell suspension containing SAC was added to all wells. The plates were then incubated for 72 hours (37° C., 5% CO₂).

After 72 hours, each well was supplemented with 50 µl of complete medium containing 0.5 µCi of 3H-thymidine (6.7 Ci/mM; Amersham) and cells were incubated for an additional 20-24 hours at (37° C., 5% CO₂). Following incubation cells were harvested using a Tomtec Cell Harvester and filters counted in a TopCount Scintillation counter (Packard).

Example 22

Human B Cell Proliferation Assay for In Vitro Screening of B Lymphocyte Stimulator Antagonist Molecules

The bioassay for assessing the effects of putative B Lymphocyte Stimulator antagonists was performed in triplicate in 96 well format by mixing equal volumes of B Lymphocyte Stimulator, responder cells, and putative antagonist each of which is prepared as a 3x stock reagent.

B-lymphocytes were purified from human tonsil by MACS (anti-CD3 depletion), washed, and resuspended in complete medium (CM) (RPMI 1640 with 10% FBS containing 100U/ml penicillin, 100 µg/ml streptomycin, 4 mM glutamine, 5x10⁻⁵ M beta-mercaptoethanol) at a concentration of 3x10⁶ cells/mL. *Staphylococcus aureus*, Cowan I (SAC, CalBiochem) was added to cells at 3x concentration (3x=1:33,333 dilution of stock).

Meanwhile, eight serial dilutions (3-fold) of potential antagonist were prepared in CM such that the diluted antagonists are at 3x the final concentrations to be tested in the assay.

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Antibodies are routinely tested starting at a final concentration of 10 $\mu\text{g/mL}$ and going down to about 1.5 ng/mL .

Human rB Lymphocyte Stimulator was prepared in CM to 3 \times concentration (3 \times =300 ng/mL , 30 ng/mL , and 3 ng/mL) in CM. Potential inhibitors were routinely tested at several concentrations of B Lymphocyte Stimulator to avoid false negatives due to unexpectedly low affinity or antagonist concentration.

Fifty microliters of diluted antagonist and 50 μL of diluted B Lymphocyte Stimulator were added to the putative antagonist dilution series.

Cells were then incubated for 72 hours (37° C., 5% CO_2) in a fully humidified chamber. After 72 hrs., the cells were

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supplemented with 0.5 $\mu\text{Ci/well}$ 3H-thymidine (6.7 Ci/mmol) and incubated for an additional 24 hours. Plates were harvested using a Tomtec Cell Harvester and filters counted in a TopCount Scintillation counter (Packard).

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in this application is incorporated in their entireties herein by reference. Further, the sequences disclosed herein are also disclosed in U.S. Provisional Application 60/212,210 filed Jun. 16, 2000 the contents of which are incorporated in their entireties herein by reference.

TABLE 1

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator

Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I003F12S	1	138-248	160-173	189-195	228-237	1-122	26-35	50-66	99-111 HDDDLVTGYFES	(SEQ ID NO:2130)
I006D08	2	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112 SRDLLLPHYGMDV	(SEQ ID NO:2133)
I008A11	3	144-254	166-179	195-201	234-243	1-128	26-37	52-69	102-117 DRYDILTGYYGYGMDV	(SEQ ID NO:2129)
I017D10	4	148-255	169-179	195-201	234-244	1-132	26-35	50-66	99-121 VQMDSEYDILLTGINVGPIYFDY	(SEQ ID NO:2132)
I022D01	5	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115 DGYDILTGYSYGYGMDV	(SEQ ID NO:2135)
I031F02	6	138-251	160-173	189-195	228-240	1-121	26-35	50-66	99-110 GYDSSAFRAFDI	(SEQ ID NO:2136)
I050A12	7	142-250	164-174	190-196	229-239	1-124	26-35	50-66	99-113 APYDLLTHYFHYFDY	(SEQ ID NO:2134)
I051C04	8	146-256	168-181	197-203	236-245	1-129	26-35	50-66	99-118 AATTSQKHNYATYFYGMDV	(SEQ ID NO:2131)
I050B11	9	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTSYVFQYFDH	(SEQ ID NO:2137)
I050B11-01	10	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTSYVFQWVA	(SEQ ID NO:2143)
I050B11-02	11	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTSYVFQWVA	(SEQ ID NO:2143)
I050B11-03	12	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTRYVFQYFDH	(SEQ ID NO:2144)
I050B11-04	13	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTRYVFQYFDH	(SEQ ID NO:2141)
I050B11-05	14	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTRYVFQWVA	(SEQ ID NO:2142)
I050B11-06	15	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTRYVFQWVA	(SEQ ID NO:2140)
I050B11-07	16	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTRYVFQYFDH	(SEQ ID NO:2144)
I050B11-08	17	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTRYVFQYFDH	(SEQ ID NO:2141)
I050B11-09	18	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTRYVFQWVA	(SEQ ID NO:2142)
I050B11-10	19	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTRYVFQWVA	(SEQ ID NO:2142)
I050B11-11	20	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTRYVFQWVA	(SEQ ID NO:2140)
I050B11-12	21	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTRYVFQWVA	(SEQ ID NO:2140)
I050B11-13	22	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTSYVFQYFDH	(SEQ ID NO:2137)
I050B11-14	23	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTSYVFQYFDH	(SEQ ID NO:2137)
I050B11-15	24	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTSYVFQWVA	(SEQ ID NO:2143)
I050B11-16	25	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTSYVFQWVA	(SEQ ID NO:2143)
I050B11-17	26	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTRYVFQYFDH	(SEQ ID NO:2144)
I050B11-18	27	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTRYVFQYFDH	(SEQ ID NO:2144)
I050B11-19	28	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDILTSYVFQYFDH	(SEQ ID NO:2139)
I050B11-20	29	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDILTSYVFQYFDH	(SEQ ID NO:2139)
I050B11-21	30	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDILTRYVFQYFDH	(SEQ ID NO:2138)
I050B11-22	31	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDILTRYVFQYFDH	(SEQ ID NO:2138)
I050B11-23	32	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDILTRYVFQYFDH	(SEQ ID NO:2138)
I050B11-24	33	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDILTSYVFQYFDH	(SEQ ID NO:2139)
I050B11-25	34	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTRYVFQYFDH	(SEQ ID NO:2144)
I050B11-26	35	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDILTSYVFQYFDH	(SEQ ID NO:2139)
I050B11-27	36	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDILTRYVFQYFDH	(SEQ ID NO:2138)
I050B11-28	37	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTSYVFQYFDH	(SEQ ID NO:2137)
I093D03	38	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTSYVLGYLS	(SEQ ID NO:2145)
I093D09	39	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTSYVFQYFDH	(SEQ ID NO:2137)
I093G08	40	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTSYVFQWVA	(SEQ ID NO:2143)
I097D11	41	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDILTSYVFQYFDH	(SEQ ID NO:2139)
I101A04	42	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTSYVFQYFDH	(SEQ ID NO:2137)
I101B01	43	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTSYVFQYFDH	(SEQ ID NO:2137)
I102A02	44	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTSYVFQYFDH	(SEQ ID NO:2137)
I102E01	45	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114 PFYDTLTRYVFQYFDH	(SEQ ID NO:2144)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I102G06	46	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTGYVFQYFDH (SEQ ID NO:2141)
I087A07	47	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLPKRVIP (SEQ ID NO:2227)
I087A08	48	142-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDTLTSYVCRPHF (SEQ ID NO:2238)
I087A09	49	142-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDTLTSYVRCPPV (SEQ ID NO:2272)
I087B02	50	142-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDTLTSYVFRPDL (SEQ ID NO:2281)
I087B03	51	142-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDTLTSYVKSMPT (SEQ ID NO:2305)
I087B04	52	142-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDTLTSYVPLLYC (SEQ ID NO:2292)
I087B05	53	142-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDTLTSYVFPVST (SEQ ID NO:2270)
I087B06	54	142-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDTLTSYVGINGL (SEQ ID NO:2282)
I087B08	55	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVPCSPPR (SEQ ID NO:2261)
I087B09	56	142-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDTLTSYVCYPPA (SEQ ID NO:2240)
I087C02	57	142-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDTLTSYVPLLS (SEQ ID NO:2224)
I087C05	58	142-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDTLTSYVALYRL (SEQ ID NO:2234)
I087C06	59	142-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDTLTSYVRASF (SEQ ID NO:2271)
I087C07	60	142-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDTLTSYVCTPVP (SEQ ID NO:2319)
I087C08	61	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVWSPFFS (SEQ ID NO:2277)
I087D01	62	142-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDTLTSYVTPRGY (SEQ ID NO:2275)
I087D02	63	142-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDTLTSYVSSLLS (SEQ ID NO:2213)
I087D03	64	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVPLPLC (SEQ ID NO:2263)
I087D05	65	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVPPPSFL (SEQ ID NO:2266)
I087D07	66	142-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDTLTSYVPTSTT (SEQ ID NO:2269)
I087D09	67	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVISCWA (SEQ ID NO:2299)
I087E04	68	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVSALPPP (SEQ ID NO:2274)
I087E05	69	142-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDTLTSYVCRHLF (SEQ ID NO:2236)
I087E10	70	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVWSPFSL (SEQ ID NO:2307)
I087F02	71	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVMGVTPS (SEQ ID NO:2322)
I087F04	72	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLFKPV (SEQ ID NO:2326)
I087F05	73	142-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDTLTSYVPSVGG (SEQ ID NO:2267)
I087F07	74	142-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDTLTSYVPPTRH (SEQ ID NO:2286)
I087F08	75	142-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDTLTSYVLRSD (SEQ ID NO:2243)
I087F09	76	142-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDTLTSYVPLPLH (SEQ ID NO:2310)
I087G05	77	142-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDTLTSYVLRCLV (SEQ ID NO:2239)
I087G06	78	142-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDTLTSYVHPSRS (SEQ ID NO:2285)
I087G07	79	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLRPLPQ (SEQ ID NO:2241)
I087G09	80	142-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDTLTSYVGPYGT (SEQ ID NO:2284)
I087G10	81	142-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDTLTSYVTTPTCT (SEQ ID NO:2276)
I087H02	82	137-244	160-170	186-192	225-233	1-121	26-35	50-66	99-110	ASYLSTSSSLDN (SEQ ID NO:2265)
I088A01	83	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I088A03	84	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVIPFLPL (SEQ ID NO:2290)
I088A04	85	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLHIYPH (SEQ ID NO:2335)
I088A08	86	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTNYVFEEYAS (SEQ ID NO:2323)
I088A09	87	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVILYYLH (SEQ ID NO:2295)
I088A10	88	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I088A11	89	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLMYFPH (SEQ ID NO:2220)
I088A12	90	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLPFYPL (SEQ ID NO:2325)
I088B01	91	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)

TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I088B02	92	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFDDYAS (SEQ ID NO:2244)
I088B03	93	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVIFPLPL (SEQ ID NO:2290)
I088B05	94	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I088B06	95	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFEYYSL (SEQ ID NO:2324)
I088B07	96	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I088B08	97	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I088B09	98	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLEFYLL (SEQ ID NO:2303)
I088B10	99	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I088B12	100	142-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDTLTSYVLPDLS (SEQ ID NO:2223)
I088C01	101	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLYFVPS (SEQ ID NO:2317)
I088C03	102	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I088C09	103	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I088C12	104	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I088D01	105	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I088D03	106	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLYHYAL (SEQ ID NO:2215)
I088D04	107	142-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDTLTSYVLPSPV (SEQ ID NO:2225)
I088D07	108	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I088D08	109	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I088D11	110	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I088E01	111	140-248	163-174	190-196	229-237	1-122	23-32	47-63	96-111	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I088E02	112	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLYHYLY (SEQ ID NO:2216)
I088E03	113	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I088E04	114	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I088E08	115	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I088E10	116	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I088E11	117	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I088F07	118	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I088G02	119	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I088G03	120	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I088G07	121	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFHYPL (SEQ ID NO:2260)
I088G09	122	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPPVYL (SEQ ID NO:2264)
I088G10	123	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLFIDH (SEQ ID NO:2301)
I088H05	124	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I088H07	125	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I092A03	126	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I092A05	127	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFHYVDV (SEQ ID NO:2258)
I092A06	128	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I092A08	129	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVHEFFSL (SEQ ID NO:2283)
I092A10	130	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I092A11	131	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I092B01	132	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I092B02	133	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I092B04	134	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I092B05	135	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I092B10	136	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I092B12	137	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I092C01	138	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPQYFDH (SEQ ID NO:2137)
I092C02	139	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPQYFDH (SEQ ID NO:2137)
I092C07	140	142-250	165-176	192-198	231-239	1-124	26-35	50-66	99-113	PFYDTLTSYVLALDL (SEQ ID NO:2328)
I092C08	141	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFGYYSL (SEQ ID NO:2254)
I092C12	142	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPQYFDH (SEQ ID NO:2137)
I092D01	143	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLKYYTD (SEQ ID NO:2226)
I092D07	144	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPQYFDH (SEQ ID NO:2137)
I092D09	145	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVMHAYPL (SEQ ID NO:2255)
I092D10	146	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVPHLPV (SEQ ID NO:2256)
I092D11	147	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPQYFDH (SEQ ID NO:2137)
I092E01	148	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPQYFDH (SEQ ID NO:2137)
I092E03	149	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYAFQYFDH (SEQ ID NO:2230)
I092E04	150	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFEYFSV (SEQ ID NO:2248)
I092E07	151	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPQYFDH (SEQ ID NO:2137)
I092E10	152	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLPYYPL (SEQ ID NO:2327)
I092E11	153	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPQYFDH (SEQ ID NO:2137)
I092F01	154	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPQYFDH (SEQ ID NO:2137)
I092F02	155	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPQYFDH (SEQ ID NO:2137)
I092F05	156	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPQYFDH (SEQ ID NO:2137)
I092F07	157	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPQYFDH (SEQ ID NO:2137)
I092F08	158	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPQYFDH (SEQ ID NO:2137)
I092F11	159	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPQYFDH (SEQ ID NO:2137)
I092F12	160	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLPAYPD (SEQ ID NO:2306)
I092G01	161	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPQYFDH (SEQ ID NO:2137)
I092G05	162	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPQYFDH (SEQ ID NO:2137)
I092G10	163	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPQYFDH (SEQ ID NO:2137)
I092H01	164	137-244	160-170	186-192	225-233	1-121	26-35	50-66	99-110	ASVLTSSSSLDN (SEQ ID NO:2265)
I093A06	165	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLPVYDH (SEQ ID NO:2334)
I093A09	166	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPQYFAH (SEQ ID NO:2268)
I093A11	167	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPQYFDH (SEQ ID NO:2137)
I093A12	168	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPQYFDH (SEQ ID NO:2137)
I093B02	169	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPQYFDH (SEQ ID NO:2137)
I093B05	170	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVIFYYPT (SEQ ID NO:2289)
I093B06	171	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPQYFDH (SEQ ID NO:2137)
I093B09	172	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLEVYHP (SEQ ID NO:2318)
I093B12	173	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFAPLVT (SEQ ID NO:2242)
I093C02	174	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLAHAYAF (SEQ ID NO:2332)
I093C03	175	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPQYFDH (SEQ ID NO:2137)
I093C05	176	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVILYYLH (SEQ ID NO:2295)
I093D05	177	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFEFLPL (SEQ ID NO:2245)
I093D08	178	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVRPFYAH (SEQ ID NO:2273)
I093D10	179	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPQYFDH (SEQ ID NO:2137)
I093D12	180	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLAHFYRV (SEQ ID NO:2302)
I093E01	181	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPQYFDH (SEQ ID NO:2137)
I093E02	182	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPQYFDH (SEQ ID NO:2297)
I093E05	183	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVHEFFSL (SEQ ID NO:2283)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I093E08	184	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVMQFFPT (SEQ ID NO:2321)
I093E10	185	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLSFYFV (SEQ ID NO:2246)
I093F01	186	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLYYYAF (SEQ ID NO:2251)
I093F03	187	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVVFQYFDH (SEQ ID NO:2137)
I093F05	188	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVVFQYFDH (SEQ ID NO:2137)
I093F08	189	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVVFQYFDH (SEQ ID NO:2137)
I093F11	190	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLHFYPL (SEQ ID NO:2333)
I093G07	191	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLQYYVL (SEQ ID NO:2237)
I093G11	192	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVVFQYFDH (SEQ ID NO:2137)
I093G12	193	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVVFQYFDH (SEQ ID NO:2137)
I093H06	194	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVVFQYFDH (SEQ ID NO:2137)
I094A08	195	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVVFQYFDY (SEQ ID NO:2280)
I094B07	196	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLPVWVS (SEQ ID NO:2228)
I094B08	197	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVVFQYFDH (SEQ ID NO:2137)
I094B12	198	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVVFQYFDH (SEQ ID NO:2137)
I094C11	199	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVVFQYFDH (SEQ ID NO:2137)
I094C12	200	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVVFQYFDH (SEQ ID NO:2137)
I094D06	201	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVIEYYFV (SEQ ID NO:2288)
I094D07	202	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVVFQYFDH (SEQ ID NO:2137)
I094D08	203	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLHLYPL (SEQ ID NO:2314)
I094D09	204	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVVFQYFDH (SEQ ID NO:2137)
I094D10	205	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVVFQYFDH (SEQ ID NO:2137)
I094D11	206	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVVFHYFV (SEQ ID NO:2218)
I094E04	207	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVVFQYFDH (SEQ ID NO:2137)
I094E08	208	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLEAFSL (SEQ ID NO:2311)
I094F04	209	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFGFYFV (SEQ ID NO:2252)
I094F05	210	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVVFQYFDH (SEQ ID NO:2137)
I094F10	211	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVVFQYFDH (SEQ ID NO:2278)
I094F11	212	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLWYYQD (SEQ ID NO:2249)
I094F12	213	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVIFPYPL (SEQ ID NO:2296)
I094G06	214	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVVFQYFDH (SEQ ID NO:2137)
I094G10	215	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVVFQYFDH (SEQ ID NO:2137)
I095A04	216	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVVFQYFDH (SEQ ID NO:2137)
I095A12	217	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLEYFPL (SEQ ID NO:2320)
I095B04	218	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLEFFPA (SEQ ID NO:2312)
I095B09	219	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVIEYLPV (SEQ ID NO:2287)
I095B10	220	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLHYYSA (SEQ ID NO:2217)
I095C02	221	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLFYYTA (SEQ ID NO:2331)
I095C05	222	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLHLYLPV (SEQ ID NO:2337)
I095C07	223	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVVFQYFDH (SEQ ID NO:2137)
I095C08	224	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVVFQYFDH (SEQ ID NO:2137)
I095C09	225	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVMHYFPT (SEQ ID NO:2259)
I095D01	226	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVVFQYFDH (SEQ ID NO:2137)
I095D02	227	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLQYFRY (SEQ ID NO:2235)
I095D03	228	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLQVFDT (SEQ ID NO:2233)
I095D05	229	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVVFQYFDH (SEQ ID NO:2137)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I095D09	230	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I095E01	231	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLDYYSS (SEQ ID NO:2309)
I095E05	232	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDALTSYVFQYFDH (SEQ ID NO:2221)
I095E12	233	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I095F06	234	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFPFYPH (SEQ ID NO:2262)
I095F09	235	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVIGFYFV (SEQ ID NO:2291)
I095G06	236	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I095G09	237	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVMDFFYSV (SEQ ID NO:2253)
I095G11	238	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I096A01	239	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I096A10	240	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLPFYAL (SEQ ID NO:2222)
I096B01	241	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I096B03	242	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I096C01	243	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I096C06	244	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLPYLTH (SEQ ID NO:2229)
I096C09	245	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I096D01	246	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I096D02	247	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I096D05	248	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I096D06	249	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I096D09	250	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I096E02	251	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLFYFV (SEQ ID NO:2329)
I096E06	252	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLHYHTH (SEQ ID NO:2336)
I096E11	253	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I096F02	254	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVHFLPL (SEQ ID NO:2330)
I096G01	255	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVIFFLPL (SEQ ID NO:2290)
I096G02	256	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I096G05	257	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I096G07	258	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I096G09	259	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVMHYLPV (SEQ ID NO:2257)
I096G12	260	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLEFFSH (SEQ ID NO:2315)
I096H01	261	137-244	160-170	186-192	225-233	1-121	26-35	50-66	99-110	ASYLSTSSSLDN (SEQ ID NO:2265)
I097A04	262	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVIHLYVT (SEQ ID NO:2294)
I097A06	263	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLPYYTL (SEQ ID NO:2231)
I097A09	264	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLHYIPI (SEQ ID NO:2298)
I097B02	265	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLFYFPL (SEQ ID NO:2247)
I097B09	266	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I097B10	267	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I097B11	268	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I097C05	269	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLHYIYTH (SEQ ID NO:2219)
I097C09	270	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLHYIYAY (SEQ ID NO:2316)
I097C11	271	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I097D05	272	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVIHFYSL (SEQ ID NO:2293)
I097D06	273	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFGFFPH (SEQ ID NO:2300)
I097E01	274	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I097E04	275	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I097E08	276	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I097E09	277	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I097F09	278	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I097G10	279	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFAH (SEQ ID NO:2268)
I097H02	280	137-244	160-170	186-192	225-233	1-121	26-35	50-66	99-110	ASYLSTSSSLDN (SEQ ID NO:2265)
I098A04	281	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I098A05	282	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I098B08	283	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLDYFSV (SEQ ID NO:2308)
I098C01	284	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PIYDTLTSYVFQYFDH (SEQ ID NO:2278)
I098C04	285	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLYYAP (SEQ ID NO:2251)
I098F11	286	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I098F12	287	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFFYYP (SEQ ID NO:2250)
I098G02	288	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I098G12	289	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I098H05	290	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I101A01	291	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I101B04	292	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I101B06	293	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVIPFLTH (SEQ ID NO:2304)
I101D04	294	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLEFPDP (SEQ ID NO:2313)
I101D07	295	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I101E09	296	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDR (SEQ ID NO:2279)
I101E12	297	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I101G02	298	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I101G11	299	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I102C03	300	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I102E09	301	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I102F02	302	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I102G08	303	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I102G09	304	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVLYHYAH (SEQ ID NO:2214)
I106A09	305	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I106B02	306	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I106B06	307	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I106C07	308	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I106E05	309	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I106E12	310	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I106G01	311	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I106G03	312	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I109B06	313	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I109D12	314	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I109E12	315	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I109G06	316	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I109H04	317	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I110B03	318	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I112D09	319	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYGFQYFDH (SEQ ID NO:2232)
I112F10	320	143-251	166-177	193-199	232-240	1-125	26-35	50-66	99-114	PFYDTLTSYVFQYFDH (SEQ ID NO:2137)
I089F12	321	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPFHGLDS (SEQ ID NO:2146)

TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator											
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)	
I105E12	322	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPHHSFDL	(SEQ ID NO:2147)
I108D08	323	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPAPLYP	(SEQ ID NO:2148)
I108E06	324	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPHHGLDV	(SEQ ID NO:2151)
I113E07	325	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPHHSDDL	(SEQ ID NO:2152)
I114G05	326	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPHHSFDL	(SEQ ID NO:2147)
I116A01	327	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPHHALS	(SEQ ID NO:2149)
I116A09	328	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPHHSFDL	(SEQ ID NO:2150)
I116C11	329	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPHHSFDL	(SEQ ID NO:2147)
I085A01	330	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPHDLHLF	(SEQ ID NO:2602)
I085A02	331	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPSDPLGF	(SEQ ID NO:2639)
I085A03	332	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPHPLSF	(SEQ ID NO:2561)
I085A04	333	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPAPLFF	(SEQ ID NO:2550)
I085A05	334	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPSDPLSL	(SEQ ID NO:2659)
I085A06	335	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPSAPLSF	(SEQ ID NO:2611)
I085A07	336	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPASPLSF	(SEQ ID NO:2390)
I085A09	337	140-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111	SRDLLLLPPNDALS	(SEQ ID NO:2632)
I085A10	338	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPSAPLRF	(SEQ ID NO:2609)
I085A11	339	140-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111	SRDLLLLPPHDPLE	(SEQ ID NO:2363)
I085B01	340	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPQSPLYP	(SEQ ID NO:2466)
I085B02	341	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPHSSLVF	(SEQ ID NO:2392)
I085B03	342	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPYDPLLF	(SEQ ID NO:2638)
I085B04	343	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPHAPLYP	(SEQ ID NO:2589)
I085B05	344	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPHAPLSP	(SEQ ID NO:2573)
I085B06	345	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPSLPLSF	(SEQ ID NO:2574)
I085B07	346	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPDFMAP	(SEQ ID NO:2433)
I085B10	347	140-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111	SRDLLLLPPHSPLY	(SEQ ID NO:2470)
I085B12	348	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPQDPLSP	(SEQ ID NO:2372)
I085C02	349	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPDDPLLS	(SEQ ID NO:2430)
I085C03	350	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPHGPLLI	(SEQ ID NO:2400)
I085C05	351	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPGSPLLF	(SEQ ID NO:2491)
I085C06	352	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPTAALSF	(SEQ ID NO:2341)
I085C07	353	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPHTPLRF	(SEQ ID NO:2375)
I085C09	354	140-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111	SRDLLLLPPHSPLT	(SEQ ID NO:2468)
I085C10	355	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPFSPLLF	(SEQ ID NO:2471)
I085C12	356	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPSHPLFP	(SEQ ID NO:2680)
I085D01	357	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPRLPLLF	(SEQ ID NO:2548)
I085D02	358	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPSQYLDL	(SEQ ID NO:2523)
I085D03	359	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPSSPLLF	(SEQ ID NO:2713)
I085D04	360	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPYFPLVF	(SEQ ID NO:2646)
I085D06	361	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPGSPLLD	(SEQ ID NO:2488)
I085D07	362	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPQAPLFF	(SEQ ID NO:2694)
I085D08	363	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPHSYLSF	(SEQ ID NO:2477)
I085D09	364	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPQTPLFP	(SEQ ID NO:2467)
I085D10	365	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPHSPLHP	(SEQ ID NO:2563)
I085D11	366	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPHAPLAP	(SEQ ID NO:2510)
I085D12	367	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPHTLRF	(SEQ ID NO:2495)

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scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I085E01	368	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPYAVLHP (SEQ ID NO:2620)
I085E02	369	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPPTSPLRL (SEQ ID NO:2575)
I085E07	370	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDALSF (SEQ ID NO:2568)
I085E08	371	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPNAPLDP (SEQ ID NO:2603)
I085E09	372	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPPRF (SEQ ID NO:2628)
I085E10	373	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPSEPLWP (SEQ ID NO:2668)
I085E11	374	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPSSPLSN (SEQ ID NO:2716)
I085E12	375	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPPLPLTP (SEQ ID NO:2431)
I085F01	376	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPSPSLFP (SEQ ID NO:2551)
I085F02	377	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPPTSPLQL (SEQ ID NO:2376)
I085F03	378	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPYTPLLF (SEQ ID NO:2682)
I085F04	379	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPSSPLAF (SEQ ID NO:2707)
I085F05	380	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLVF (SEQ ID NO:2706)
I085F06	381	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPSSAHLFP (SEQ ID NO:2586)
I085F07	382	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPAGPLRF (SEQ ID NO:2410)
I085F09	383	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDHAFFV (SEQ ID NO:2439)
I085F10	384	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPSSDSGFA (SEQ ID NO:2662)
I085F11	385	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPSSYLEF (SEQ ID NO:2339)
I085F12	386	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPFRDPLII (SEQ ID NO:2558)
I085G01	387	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPSPALHP (SEQ ID NO:2605)
I085G02	388	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPNAPLLL (SEQ ID NO:2613)
I085G03	389	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPAPLFP (SEQ ID NO:2403)
I085G04	390	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPSPALDP (SEQ ID NO:2601)
I085G07	391	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPNAVLDI (SEQ ID NO:2629)
I085G08	392	141-249	163-173	189-195	228-238	1-323	26-35	50-66	99-112	SRDLLLPSEPLFF (SEQ ID NO:2664)
I085G09	393	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPSSVLWP (SEQ ID NO:2338)
I085G10	394	140-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111	SRDLLLPAPLQ (SEQ ID NO:2554)
I085G11	395	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLAP (SEQ ID NO:2445)
I085G12	396	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPSSPLHP (SEQ ID NO:2576)
I085H10	397	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	DGYDILTGYSYGMDV (SEQ ID NO:2135)
I086A03	398	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPSPMLTF (SEQ ID NO:2695)
I086A04	399	141-249	163-173	189-195	228-238	1-323	26-35	50-66	99-112	SRDLLLPSPSLHP (SEQ ID NO:2438)
I086A05	400	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPAPLSP (SEQ ID NO:2569)
I086A07	401	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDAPLRF (SEQ ID NO:2421)
I086A09	402	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPSSHLFP (SEQ ID NO:2704)
I086A10	403	141-249	163-173	189-195	228-238	1-323	26-35	50-66	99-112	SRDLLLPSPALSS (SEQ ID NO:2624)
I086A11	404	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPAPLTP (SEQ ID NO:2577)
I086A12	405	141-249	163-173	189-195	228-238	1-323	26-35	50-66	99-112	SRDLLLPYDPLHS (SEQ ID NO:2635)
I086B02	406	141-249	163-173	189-195	228-238	1-323	26-35	50-66	99-112	SRDLLLPDPLHP (SEQ ID NO:2348)
I086B03	407	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPAPLFP (SEQ ID NO:2412)
I086B05	408	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPPEPLII (SEQ ID NO:2457)
I086B06	409	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPAPLNP (SEQ ID NO:2364)
I086B07	410	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPSSPLVF (SEQ ID NO:2720)
I086B09	411	141-249	163-173	189-195	228-238	1-323	26-35	50-66	99-112	SRDLLLPPTSPLSF (SEQ ID NO:2579)
I086B10	412	141-249	163-173	189-195	228-238	1-323	26-35	50-66	99-112	SRDLLLPDGLSS (SEQ ID NO:2428)
I086B11	413	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPISPLCF (SEQ ID NO:2530)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I086C03	414	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPPTAPLYG (SEQ ID NO:2535)
I086C05	415	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPFHSLFF (SEQ ID NO:2427)
I086C07	416	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPQGLRF (SEQ ID NO:2440)
I086C08	417	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPAAPLAF (SEQ ID NO:2401)
I086C09	418	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPPLPLF (SEQ ID NO:2350)
I086C10	419	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPFTPLIF (SEQ ID NO:2541)
I086C11	420	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPDDPLSF (SEQ ID NO:2432)
I086C12	421	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPPTDCLF (SEQ ID NO:2622)
I086D01	422	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPSPALTP (SEQ ID NO:2630)
I086D04	423	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLYD (SEQ ID NO:2697)
I086D05	424	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPSPSLF (SEQ ID NO:2461)
I086D06	425	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPAPLDL (SEQ ID NO:2379)
I086D07	426	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPHTLTF (SEQ ID NO:2365)
I086D08	427	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPSSLDF (SEQ ID NO:2473)
I086D09	428	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPNHPMPF (SEQ ID NO:2665)
I086D10	429	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPPLSLF (SEQ ID NO:2587)
I086D11	430	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPNAPLRF (SEQ ID NO:2610)
I086D12	431	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPRAHLRF (SEQ ID NO:2469)
I086E02	432	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYDPLHF (SEQ ID NO:2621)
I086E03	433	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPDALQS (SEQ ID NO:2598)
I086E05	434	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPRTPLTF (SEQ ID NO:2567)
I086E07	435	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPAAHLSF (SEQ ID NO:2398)
I086E08	436	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPAPLRF (SEQ ID NO:2490)
I086E09	437	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPSPPLAP (SEQ ID NO:2464)
I086E10	438	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPAPLDF (SEQ ID NO:2367)
I086E12	439	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPPTAPLRF (SEQ ID NO:2522)
I086F02	440	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPSSPLRI (SEQ ID NO:2714)
I086F05	441	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPTEPLQF (SEQ ID NO:2540)
I086F08	442	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPSPDPLSA (SEQ ID NO:2643)
I086F09	443	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYNPPIF (SEQ ID NO:2653)
I086F11	444	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPHTPLLF (SEQ ID NO:2489)
I086G03	445	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPAPLDL (SEQ ID NO:2513)
I086G04	446	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPFDPLLI (SEQ ID NO:2454)
I086G05	447	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPPTDALRI (SEQ ID NO:2537)
I086G06	448	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPAPLRF (SEQ ID NO:2407)
I086G07	449	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPSPGLLF (SEQ ID NO:2448)
I086G09	450	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYAPLSF (SEQ ID NO:2385)
I086G10	451	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPADSLF (SEQ ID NO:2391)
I086H05	452	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYSPLTH (SEQ ID NO:2679)
I089A01	453	140-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111	SRDLLFPDPLI (SEQ ID NO:2612)
I089A03	454	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPPLPLLI (SEQ ID NO:2590)
I089A06	455	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPHTPLHF (SEQ ID NO:2485)
I089A07	456	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPPTDALYF (SEQ ID NO:2539)
I089A08	457	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPYTPPLF (SEQ ID NO:2682)
I089A10	458	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPHQPLTF (SEQ ID NO:2436)
I089A11	459	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLFPRTYLDL (SEQ ID NO:2572)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator											
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)	
I089B01	460	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHSPLHS	(SEQ ID NO:2450)
I089B02	461	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHSPDL	(SEQ ID NO:2147)
I089B03	462	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSTPLQP	(SEQ ID NO:2528)
I089B04	463	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSTPLLF	(SEQ ID NO:2556)
I089B05	464	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSSPLIF	(SEQ ID NO:2712)
I089B06	465	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPMAPLSP	(SEQ ID NO:2596)
I089B07	466	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPYSGLDA	(SEQ ID NO:2374)
I089B08	467	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPAPLSP	(SEQ ID NO:2405)
I089B09	468	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPKSPILF	(SEQ ID NO:2384)
I089B10	469	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSTPLFF	(SEQ ID NO:2571)
I089B11	470	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNSPLFP	(SEQ ID NO:2388)
I089C01	471	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHYGMDV	(SEQ ID NO:2133)
I089C02	472	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSPPLLF	(SEQ ID NO:2551)
I089C03	473	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPYHPLLF	(SEQ ID NO:2532)
I089C05	474	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSSALRP	(SEQ ID NO:2722)
I089C06	475	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSPYLSF	(SEQ ID NO:2701)
I089C07	476	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPQAPLFD	(SEQ ID NO:2683)
I089C09	477	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHPPTF	(SEQ ID NO:2507)
I089D01	478	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHPAPLV	(SEQ ID NO:2581)
I089D02	479	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHYGMDV	(SEQ ID NO:2133)
I089D03	480	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHYPLLF	(SEQ ID NO:2344)
I089D04	481	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSSPLSP	(SEQ ID NO:2717)
I089D05	482	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHPAPLFT	(SEQ ID NO:2546)
I089D07	483	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNDPLLI	(SEQ ID NO:2634)
I089D08	484	140-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111	SRDLLLFPHPAPLQ	(SEQ ID NO:2554)
I089D09	485	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSPHAPHE	(SEQ ID NO:2677)
I089D11	486	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNHPLYP	(SEQ ID NO:2663)
I089E01	487	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPYSPLFP	(SEQ ID NO:2657)
I089E02	488	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPQDPLHP	(SEQ ID NO:2346)
I089E03	489	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPDAPLFP	(SEQ ID NO:2423)
I089E04	490	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHSPLLI	(SEQ ID NO:2453)
I089E06	491	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSPPLLF	(SEQ ID NO:2491)
I089E09	492	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSSPLTF	(SEQ ID NO:2718)
I089E10	493	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSTPLSF	(SEQ ID NO:2566)
I089E11	494	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPPLSPWLP	(SEQ ID NO:2578)
I089F01	495	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSTPLLF	(SEQ ID NO:2380)
I089F03	496	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHPDPLLI	(SEQ ID NO:2580)
I089F04	497	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPYSPLLF	(SEQ ID NO:2670)
I089F05	498	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHSPLRI	(SEQ ID NO:2459)
I089F06	499	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPAPLPLF	(SEQ ID NO:2490)
I089F08	500	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPRTPLTF	(SEQ ID NO:2567)
I089F09	501	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPPLAPLSF	(SEQ ID NO:2555)
I089F10	502	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNQPLSF	(SEQ ID NO:2667)
I089F11	503	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPLEPMHF	(SEQ ID NO:2565)
I089G01	504	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSPAPLTF	(SEQ ID NO:2626)
I089G02	505	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSPHPLLF	(SEQ ID NO:2687)

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scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I089G03	506	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPRTPLVF (SEQ ID NO:2721)
I089G05	507	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPGPSPLTF (SEQ ID NO:2389)
I089G06	508	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPPTAPLLF (SEQ ID NO:2514)
I089G07	509	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSPALDF (SEQ ID NO:2597)
I089G08	510	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSPHPLSF (SEQ ID NO:2688)
I089G11	511	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSPFLLF (SEQ ID NO:2671)
I089H10	512	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	DGYDILTGYSYIGMOV (SEQ ID NO:2135)
I090A02	513	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPAPKPLLF (SEQ ID NO:2416)
I090A03	514	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNSTLSF (SEQ ID NO:2678)
I090A04	515	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPDAPLTP (SEQ ID NO:2426)
I090A05	516	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHEPLLI (SEQ ID NO:2648)
I090A06	517	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPPTYPLSF (SEQ ID NO:2600)
I090A07	518	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPTEPLVL (SEQ ID NO:2479)
I090A08	519	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPPTYPLHF (SEQ ID NO:2584)
I090B01	520	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPDPLTF (SEQ ID NO:2627)
I090B03	521	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPQAPLTN (SEQ ID NO:2705)
I090B04	522	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHPALEA (SEQ ID NO:2520)
I090B05	523	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPDHPLLF (SEQ ID NO:2442)
I090B06	524	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPAPLPLSF (SEQ ID NO:2496)
I090B08	525	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPAGPLRF (SEQ ID NO:2542)
I090B11	526	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPFTPLTF (SEQ ID NO:2474)
I090B12	527	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPQHPPLSF (SEQ ID NO:2452)
I090C01	528	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSPAPIVF (SEQ ID NO:2591)
I090C02	529	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPQAPLTF (SEQ ID NO:2702)
I090C03	530	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPAPLPLRF (SEQ ID NO:2493)
I090C05	531	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPRTPLTF (SEQ ID NO:2567)
I090C06	532	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHPALDF (SEQ ID NO:2538)
I090C07	533	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHPAGFDS (SEQ ID NO:2498)
I090C08	534	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSPPLSF (SEQ ID NO:2676)
I090C10	535	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPGRPLTF (SEQ ID NO:2358)
I090D02	536	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPAPHLLF (SEQ ID NO:2408)
I090D03	537	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPPTAPLHP (SEQ ID NO:2351)
I090D04	538	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHEPLTA (SEQ ID NO:2654)
I090D05	539	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHPALPE (SEQ ID NO:2529)
I090D06	540	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPAPLPLDF (SEQ ID NO:2367)
I090D07	541	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPFGTLRF (SEQ ID NO:2462)
I090D08	542	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSSPLVF (SEQ ID NO:2723)
I090D09	543	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPDPLAF (SEQ ID NO:2505)
I090D12	544	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPPTSPLSF (SEQ ID NO:2579)
I090E04	545	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHPAPLLL (SEQ ID NO:2552)
I090E05	546	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSPAPISF (SEQ ID NO:2588)
I090E06	547	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPQGPLSF (SEQ ID NO:2443)
I090E07	548	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPGPSPLHP (SEQ ID NO:2484)
I090E09	549	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSPDPLSF (SEQ ID NO:2647)
I090E11	550	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPDGLAP (SEQ ID NO:2700)
I090E12	551	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPPTSPLTF (SEQ ID NO:2582)

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scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I090F01	552	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPNGPLHP (SEQ ID NO:2649)
I090F02	553	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPQAPLSF (SEQ ID NO:2696)
I090F03	554	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPPTAPLSF (SEQ ID NO:2526)
I090F04	555	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPFPPLQF (SEQ ID NO:2460)
I090F05	556	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPPLDPLHF (SEQ ID NO:2359)
I090F06	557	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPSEPLQL (SEQ ID NO:2666)
I090F07	558	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPFPAPLRF (SEQ ID NO:2451)
I090F08	559	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPPLHPLIF (SEQ ID NO:2570)
I090F09	560	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPFHYPLLF (SEQ ID NO:2344)
I090F10	561	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPFRDPLRI (SEQ ID NO:2527)
I090F11	562	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPSPNPLTF (SEQ ID NO:2698)
I090G01	563	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPPTAPLEI (SEQ ID NO:2347)
I090G02	564	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPFRDPLQF (SEQ ID NO:2395)
I090G04	565	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPHEPLAF (SEQ ID NO:2633)
I090G05	566	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPFRAPLAF (SEQ ID NO:2472)
I090G06	567	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPYSPLAF (SEQ ID NO:2656)
I090G07	568	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPHTPLDS (SEQ ID NO:2480)
I090G08	569	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPHTPLTF (SEQ ID NO:2492)
I090G09	570	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPSEPLRI (SEQ ID NO:2356)
I090G10	571	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPPTAPLDF (SEQ ID NO:2343)
I090G12	572	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPNRLDL (SEQ ID NO:2669)
I091A02	573	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPYDPLFM (SEQ ID NO:2724)
I091A03	574	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPFAPLYP (SEQ ID NO:2592)
I091A06	575	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPSPAPLAF (SEQ ID NO:2594)
I091A11	576	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPFHSPTTF (SEQ ID NO:2441)
I091B01	577	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPFHYPLLF (SEQ ID NO:2585)
I091B02	578	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPYAPLDF (SEQ ID NO:2361)
I091B04	579	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPFRDPLQF (SEQ ID NO:2395)
I091B05	580	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPFAPLEL (SEQ ID NO:2475)
I091B07	581	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPSPAPLTF (SEQ ID NO:2626)
I091B10	582	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPPTAPLAF (SEQ ID NO:2342)
I091B11	583	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPFHSPLDF (SEQ ID NO:2444)
I091B12	584	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPFHSPLTF (SEQ ID NO:2690)
I091C02	585	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPFAPPLVI (SEQ ID NO:2414)
I091C03	586	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPQAPLYP (SEQ ID NO:2378)
I091C04	587	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPPTAPLTF (SEQ ID NO:2531)
I091C05	588	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPPTPLHF (SEQ ID NO:2583)
I091C06	589	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPFHYPLLF (SEQ ID NO:2344)
I091C09	590	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPFHPPLSF (SEQ ID NO:2415)
I091C11	591	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPYHSYDI (SEQ ID NO:2650)
I091C12	592	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPYATLSF (SEQ ID NO:2618)
I091D01	593	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPFNSPLAP (SEQ ID NO:2672)
I091D02	594	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPFYSPLQF (SEQ ID NO:2673)
I091D04	595	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPQGPLSF (SEQ ID NO:2443)
I091D05	596	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPFDPLAP (SEQ ID NO:2606)
I091D06	597	140-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111	SRDLLLPFHSPLL (SEQ ID NO:2456)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I091D07	598	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNGALRF (SEQ ID NO:2645)
I091D09	599	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPYSPLRF (SEQ ID NO:2719)
I091E01	600	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPDAPLHP (SEQ ID NO:2425)
I091E02	601	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPQAPLFP (SEQ ID NO:2689)
I091E03	602	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSPAPLWP (SEQ ID NO:2352)
I091E04	603	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPKSLPAP (SEQ ID NO:2547)
I091E06	604	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSSPLHP (SEQ ID NO:2576)
I091E07	605	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNHPPLTF (SEQ ID NO:2661)
I091E08	606	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLDS (SEQ ID NO:2607)
I091E09	607	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPYAPLDF (SEQ ID NO:2361)
I091E10	608	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSSPLFP (SEQ ID NO:2711)
I091F01	609	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPAPLFP (SEQ ID NO:2486)
I091F03	610	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLVG (SEQ ID NO:2599)
I091F05	611	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPPLAPLHP (SEQ ID NO:2553)
I091F06	612	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPDPLGF (SEQ ID NO:2353)
I091F07	613	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHYGMDV (SEQ ID NO:2133)
I091F08	614	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPQSPLLF (SEQ ID NO:2458)
I091F09	615	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHEHLSF (SEQ ID NO:2354)
I091F10	616	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLDF (SEQ ID NO:2444)
I091F11	617	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2549)
I091F12	618	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHYGMDV (SEQ ID NO:2133)
I091G01	619	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLYP (SEQ ID NO:2386)
I091G03	620	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNDPLFG (SEQ ID NO:2355)
I091G04	621	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2478)
I091G05	622	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLWP (SEQ ID NO:2397)
I091G06	623	140-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111	SRDLLLFPNDPLR (SEQ ID NO:2637)
I091G07	624	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLDP (SEQ ID NO:2345)
I091G09	625	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLFP (SEQ ID NO:2349)
I091G10	626	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLVP (SEQ ID NO:2660)
I091G11	627	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLTF (SEQ ID NO:2389)
I091G12	628	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPYSHLEF (SEQ ID NO:2655)
I104A01	629	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLHP (SEQ ID NO:2455)
I104A07	630	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPQAPLFP (SEQ ID NO:2689)
I104A08	631	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPYAPLTF (SEQ ID NO:2617)
I104A09	632	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLHP (SEQ ID NO:2506)
I104A10	633	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLCP (SEQ ID NO:2636)
I104A11	634	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSF (SEQ ID NO:2611)
I104A12	635	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLRF (SEQ ID NO:2593)
I104B02	636	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSF (SEQ ID NO:2557)
I104B04	637	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLYP (SEQ ID NO:2387)
I104B09	638	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLQF (SEQ ID NO:2395)
I104B11	639	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLTF (SEQ ID NO:2531)
I104C01	640	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLYP (SEQ ID NO:2710)
I104C04	641	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLIF (SEQ ID NO:2417)
I104C05	642	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLLF (SEQ ID NO:2543)
I104C06	643	140-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111	SRDLLLFPNAPLE (SEQ ID NO:2524)

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scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I104C07	644	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPHPAPLHP (SEQ ID NO:2370)
I104C09	645	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPHPPLIF (SEQ ID NO:2399)
I104C11	646	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPHEPLIF (SEQ ID NO:2644)
I104D01	647	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPNHPADL (SEQ ID NO:2652)
I104D02	648	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPHTILYP (SEQ ID NO:2497)
I104D03	649	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDWPPLY (SEQ ID NO:2483)
I104D04	650	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPFHYPLFL (SEQ ID NO:2511)
I104D07	651	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPQAPLHP (SEQ ID NO:2691)
I104D08	652	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPHPAMPDP (SEQ ID NO:2595)
I104D09	653	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPAPLTF (SEQ ID NO:2500)
I104E01	654	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPAPLTF (SEQ ID NO:2502)
I104E02	655	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPSPSLFP (SEQ ID NO:2447)
I104E03	656	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPNDPLVL (SEQ ID NO:2641)
I104E05	657	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLVI (SEQ ID NO:2463)
I104E11	658	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPYAPLSF (SEQ ID NO:2385)
I104E12	659	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPASPLNP (SEQ ID NO:2364)
I104F02	660	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLSP (SEQ ID NO:2616)
I104F03	661	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLRP (SEQ ID NO:2360)
I104F04	662	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLDF (SEQ ID NO:2481)
I104F05	663	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLTF (SEQ ID NO:2402)
I104F06	664	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLSP (SEQ ID NO:2573)
I104F07	665	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPSSPLIL (SEQ ID NO:2465)
I104F10	666	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPNSPLSP (SEQ ID NO:2362)
I104F11	667	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLVF (SEQ ID NO:2708)
I104F12	668	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPKAPLVP (SEQ ID NO:2544)
I104G04	669	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLRF (SEQ ID NO:2559)
I104G05	670	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLAP (SEQ ID NO:2476)
I104G09	671	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLNF (SEQ ID NO:2518)
I104G11	672	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLSP (SEQ ID NO:2482)
I105A02	673	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLNP (SEQ ID NO:2494)
I105A03	674	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLDF (SEQ ID NO:2147)
I105A04	675	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLAP (SEQ ID NO:2487)
I105A08	676	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLYP (SEQ ID NO:2378)
I105A09	677	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLSF (SEQ ID NO:2557)
I105A11	678	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLSDI (SEQ ID NO:2692)
I105B04	679	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLHP (SEQ ID NO:2658)
I105B05	680	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLSF (SEQ ID NO:2676)
I105B07	681	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLSFDL (SEQ ID NO:2147)
I105B08	682	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLSFDL (SEQ ID NO:2147)
I105B10	683	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLNP (SEQ ID NO:2364)
I105B11	684	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLSP (SEQ ID NO:2651)
I105B12	685	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLII (SEQ ID NO:2560)
I105C02	686	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLAP (SEQ ID NO:2472)
I105C03	687	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLSF (SEQ ID NO:2715)
I105C05	688	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLGMDV (SEQ ID NO:2133)
I105C06	689	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLPDPLDF (SEQ ID NO:2367)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I105C08	690	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSPPLTF (SEQ ID NO:2562)
I105C12	691	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPQHGFDA (SEQ ID NO:2446)
I105D04	692	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPDRPLRF (SEQ ID NO:2360)
I105D06	693	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPDRPLSF (SEQ ID NO:2368)
I105D08	694	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPYAPLAF (SEQ ID NO:2608)
I105D09	695	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPAAFDV (SEQ ID NO:2619)
I105D10	696	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHEPLFP (SEQ ID NO:2640)
I105D11	697	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSPALTF (SEQ ID NO:2519)
I105E01	698	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHHSFDS (SEQ ID NO:2422)
I105E06	699	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHYGMDV (SEQ ID NO:2133)
I105E11	700	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNSPLHP (SEQ ID NO:2675)
I105F03	701	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHPHPLDS (SEQ ID NO:2409)
I105F06	702	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPQAPLHP (SEQ ID NO:2691)
I105F07	703	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSPWPLTF (SEQ ID NO:2340)
I105F09	704	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHYPLLF (SEQ ID NO:2344)
I105F12	705	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPYTYPLVF (SEQ ID NO:2604)
I105G03	706	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHPALHP (SEQ ID NO:2370)
I105G08	707	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPKHPPLVF (SEQ ID NO:2366)
I105G09	708	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSPALNP (SEQ ID NO:2364)
I105G10	709	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHHSFDA (SEQ ID NO:2419)
I105G11	710	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHPDPLLF (SEQ ID NO:2614)
I107A01	711	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHPPLVF (SEQ ID NO:2545)
I107A03	712	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPAPLPLP (SEQ ID NO:2501)
I107A06	713	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHPALDP (SEQ ID NO:2369)
I107A07	714	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2371)
I107A09	715	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPQAPLSP (SEQ ID NO:2699)
I107A12	716	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHPALSF (SEQ ID NO:2564)
I107B02	717	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHPALFP (SEQ ID NO:2533)
I107B04	718	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPASPLTF (SEQ ID NO:2420)
I107B05	719	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHYGMDV (SEQ ID NO:2133)
I107C01	720	139-247	161-171	187-193	226-236	1-121	24-33	48-64	97-110	SRDLLLFPHYPLLF (SEQ ID NO:2344)
I107C02	721	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHYGMYV (SEQ ID NO:2504)
I107C04	722	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHYPLHP (SEQ ID NO:2357)
I107C06	723	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHPALAP (SEQ ID NO:2510)
I107C08	724	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPQAPLEP (SEQ ID NO:2681)
I107C10	725	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSPAFDL (SEQ ID NO:2674)
I107D01	726	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPYAPLDF (SEQ ID NO:2361)
I107D04	727	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSF (SEQ ID NO:2625)
I107D07	728	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSPHSFDV (SEQ ID NO:2693)
I107D12	729	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHHSFDT (SEQ ID NO:2424)
I107E01	730	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPMLGLDL (SEQ ID NO:2499)
I107E05	731	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPAPLDF (SEQ ID NO:2367)
I107E07	732	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSPPLLF (SEQ ID NO:2551)
I107E09	733	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPKAPLTF (SEQ ID NO:2382)
I107F01	734	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPAPLSP (SEQ ID NO:2623)
I107F05	735	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPHPALAP (SEQ ID NO:2510)

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scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I107F09	736	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSPAPLAP (SEQ ID NO:2394)
I107F10	737	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPRTPLLF (SEQ ID NO:2373)
I107G01	738	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2371)
I107G05	739	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPSPALYP (SEQ ID NO:2387)
I107H02	740	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNHSFDL (SEQ ID NO:2147)
I107H06	741	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPAPLSP (SEQ ID NO:2496)
I107H09	742	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNPLEM (SEQ ID NO:2536)
I107H10	743	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLAP (SEQ ID NO:2510)
I108A12	744	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNHSFDL (SEQ ID NO:2147)
I108B03	745	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2515)
I108B04	746	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2396)
I108C09	747	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2353)
I108C11	748	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNHSFDL (SEQ ID NO:2429)
I108D10	749	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2364)
I108D11	750	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2364)
I108D12	751	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2709)
I108E01	752	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNHSFDL (SEQ ID NO:2147)
I108E03	753	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2393)
I108E05	754	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2533)
I108E07	755	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2369)
I108E08	756	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2344)
I108E09	757	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2623)
I108E10	758	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2509)
I108E11	759	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2516)
I108F10	760	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2371)
I108F12	761	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2508)
I108G01	762	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2360)
I108G02	763	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2381)
I108G07	764	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2476)
I108G10	765	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2429)
I108G11	766	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2377)
I108G12	767	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2377)
I108H01	768	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2512)
I108H02	769	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2615)
I108H06	770	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2147)
I108H08	771	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2364)
I111A06	772	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2691)
I111B12	773	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2147)
I111C01	774	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2449)
I111D06	775	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2515)
I111E04	776	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2147)
I111E10	777	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2691)
I111E11	778	141-250	163-173	189-195	229-239	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2344)
I111E12	779	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2150)
I111F07	780	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2501)
I111G02	781	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLFPNAPLSP (SEQ ID NO:2534)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator											
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)	
I111H10	782	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRYLLLPQHGFD	(SEQ ID NO:2703)
I113A04	783	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLPPSAPLWP	(SEQ ID NO:2352)
I113A12	784	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPQEPLAP	(SEQ ID NO:2434)
I113B06	785	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPNHPLEP	(SEQ ID NO:2411)
I113C06	786	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPNHPGDA	(SEQ ID NO:2406)
I113G04	787	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPHYPLLF	(SEQ ID NO:2344)
I113G05	788	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPYSLQL	(SEQ ID NO:2517)
I113G10	789	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPNHPQLQ	(SEQ ID NO:2413)
I113G11	790	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPHYPLLF	(SEQ ID NO:2344)
I113H06	791	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPHYPLLF	(SEQ ID NO:2344)
I113H07	792	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPNHSFDL	(SEQ ID NO:2147)
I113H09	793	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPHYTLFF	(SEQ ID NO:2525)
I114C04	794	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPNHPGDA	(SEQ ID NO:2406)
I114C12	795	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPQAPLHP	(SEQ ID NO:2691)
I114D04	796	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPHYGMDV	(SEQ ID NO:2133)
I114D06	797	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPNHSFDL	(SEQ ID NO:2147)
I114D10	798	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPYSLVL	(SEQ ID NO:2521)
I114E01	799	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPQEPLSP	(SEQ ID NO:2435)
I114E02	800	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPQESFSL	(SEQ ID NO:2437)
I114E03	801	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPKAPLTF	(SEQ ID NO:2382)
I114E11	802	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPNDSFFL	(SEQ ID NO:2383)
I114H01	803	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPNHSFDL	(SEQ ID NO:2147)
I114H06	804	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPNHALDV	(SEQ ID NO:2404)
I114H09	805	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPNHSFDL	(SEQ ID NO:2147)
I115A02	806	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRYLLLPNDSFDL	(SEQ ID NO:2684)
I115A07	807	143-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPHYPLLF	(SEQ ID NO:2344)
I115B10	808	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPNHSFDL	(SEQ ID NO:2147)
I115C05	809	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPAPLYP	(SEQ ID NO:2501)
I115C06	810	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRYLLLPNHSFDL	(SEQ ID NO:2150)
I115C08	811	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPNHSFDL	(SEQ ID NO:2147)
I115C12	812	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPNHSFDT	(SEQ ID NO:2424)
I115D07	813	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPHYPLLF	(SEQ ID NO:2344)
I115E09	814	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPNHRFDL	(SEQ ID NO:2418)
I115F06	815	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRYLLLPNHYGMDV	(SEQ ID NO:2685)
I115F07	816	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRYLLLPNHYPLLF	(SEQ ID NO:2686)
I115F12	817	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRYLLLPNHSFDL	(SEQ ID NO:2150)
I115G04	818	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPNHRFDL	(SEQ ID NO:2418)
I115G05	819	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPHYPLLF	(SEQ ID NO:2344)
I115G08	820	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPNDSFDL	(SEQ ID NO:2631)
I115H04	821	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPNHLSP	(SEQ ID NO:2503)
I115H07	822	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPHYPLLF	(SEQ ID NO:2344)
I115H09	823	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPNHRFDL	(SEQ ID NO:2418)
I116A07	824	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPYELPAP	(SEQ ID NO:2642)
I116B01	825	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPNHSFDL	(SEQ ID NO:2147)
I116B12	826	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPNHSFDL	(SEQ ID NO:2147)
I116C06	827	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112	SRDLLLLFPHYPLLF	(SEQ ID NO:2344)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I116D07	828	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112 SRDLLLFPPHHSFDL	(SEQ ID NO:2147)
I116E02	829	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112 SRDLLLFPPHHSFDL	(SEQ ID NO:2418)
I116E04	830	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112 SRDLLLFPPHHSFDL	(SEQ ID NO:2147)
I116F02	831	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112 SRYLLLFPPHHSFDL	(SEQ ID NO:2150)
I116F11	832	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112 SRDLLLFPHYPLLF	(SEQ ID NO:2344)
I116G05	833	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112 SRDLLLFPQAPLSP	(SEQ ID NO:2699)
I001C09	834	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116 DGSYDILTGYIIDNYMDV	(SEQ ID NO:2154)
I006D07	835	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 SHYDILTGLNMYWYFDL	(SEQ ID NO:2166)
I007B03	836	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116 DGSYDILTGYIIDNYMDV	(SEQ ID NO:2154)
I007F11	837	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113 DGIDILLVPAALMDV	(SEQ ID NO:2160)
I007H08	838	144-254	166-179	195-201	234-243	1-128	26-37	52-69	102-117 DRYDILTGYIIYGMNDV	(SEQ ID NO:2129)
I008A09	839	146-256	168-181	197-203	236-245	1-130	26-35	50-66	99-119 DREAYDILTGYIIYGMNDV	(SEQ ID NO:2172)
I008B01	840	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDFDI	(SEQ ID NO:2153)
I008C02	841	145-255	167-180	196-202	235-244	1-129	26-37	52-67	100-118 HVRDYDILTGYIRGHYFDY	(SEQ ID NO:2167)
I008C03	842	143-250	164-174	190-196	229-239	1-127	26-35	50-65	98-116 EGSYDILTGYIVGVGRMDV	(SEQ ID NO:2171)
I008C12	843	146-256	168-181	197-203	236-245	1-130	26-35	50-68	101-119 FNPTYDILTGYIIGGYFQH	(SEQ ID NO:2155)
I012A06	844	147-254	169-179	195-201	234-243	1-129	26-37	52-67	100-118 GRWDYDILTGEHLGYIYFDY	(SEQ ID NO:2162)
I016E05	845	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDFDI	(SEQ ID NO:2153)
I016F02	846	135-245	157-170	186-192	225-234	1-119	26-35	50-66	99-108 CMGDHYGMNDV	(SEQ ID NO:2161)
I016F04	847	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDFDI	(SEQ ID NO:2153)
I016H07	848	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 GYNDPLTSYNNWFDP	(SEQ ID NO:2163)
I018C02	849	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDFDI	(SEQ ID NO:2153)
I018C10	850	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116 DGSYDILTGYIIDNYMDV	(SEQ ID NO:2154)
I018D07	851	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116 DGSYDILTGYIIDNYMDV	(SEQ ID NO:2154)
I018H08	852	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDFDI	(SEQ ID NO:2153)
I018H09	853	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDFDI	(SEQ ID NO:2153)
I021B05	854	143-253	165-178	194-200	233-242	1-127	24-33	48-64	97-116 ECGNYDILTGYIIGNAFDI	(SEQ ID NO:2158)
I022E02	855	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDFDI	(SEQ ID NO:2157)
I026E03	856	143-251	165-175	191-197	230-240	1-125	26-35	50-66	99-114 TDYDILTGPYMGYFDP	(SEQ ID NO:2173)
I027A07	857	145-255	167-179	195-201	234-244	1-128	26-35	50-66	99-117 GGEYDILTGYIIFGLGVYDY	(SEQ ID NO:2170)
I028A06	858	142-253	164-176	192-198	231-242	1-126	26-35	50-66	99-115 GGDYDILTGLIYYGMNDV	(SEQ ID NO:2156)
I029D07	859	141-250	163-176	192-198	231-239	1-125	26-35	50-66	99-114 ATYDPLTGYSFDFDI	(SEQ ID NO:2153)
I029F11	860	143-253	165-177	193-199	232-242	1-127	26-35	50-66	99-116 DGSYDILTGYIIDNYMDV	(SEQ ID NO:2154)
I031C03	861	138-248	160-172	188-194	227-237	1-121	26-35	50-66	99-110 GYDSSAFRAFDI	(SEQ ID NO:2136)
I031C07	862	148-258	170-183	199-205	238-247	1-131	26-35	50-66	99-120 SSPPRWDALTDGSSYHSAMDV	(SEQ ID NO:2169)
I031F09	863	145-255	167-179	195-201	234-244	1-127	26-35	50-66	99-116 DEGRDLLTGYIWPFFDS	(SEQ ID NO:2168)
I031G08	864	148-259	170-182	198-204	237-248	1-131	26-35	50-66	99-120 SSPPKWDALTDGSSYHSAMDV	(SEQ ID NO:2159)
I031G10	865	148-258	170-182	198-204	237-247	1-131	26-35	50-66	99-120 SSPPKWDALTDGSSYHSAMDV	(SEQ ID NO:2165)
I031G11	866	145-255	167-179	195-201	234-244	1-127	26-35	50-66	99-116 DEGRDLLTGYIWPFFDS	(SEQ ID NO:2168)
I037E07	867	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113 DGIDILLVPAALMDV	(SEQ ID NO:2160)
I037E12	868	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113 DGIDILLVPAALMDV	(SEQ ID NO:2160)
I050A07	869	146-257	168-181	197-203	236-246	1-129	26-40	55-71	104-118 QDNDPLTGKLGFDY	(SEQ ID NO:2164)
I061D02	870	144-254	166-179	195-201	234-243	1-128	26-37	52-69	102-117 DRYDILTGYIIYGMNDV	(SEQ ID NO:2129)
I061E07	871	141-251	163-175	191-197	230-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDFDI	(SEQ ID NO:2153)
I061H01	872	146-256	168-181	197-203	236-245	1-130	26-35	50-68	101-119 FNPTYDILTGYIIGGYFQH	(SEQ ID NO:2155)
I001A03	873	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117 ERHYDILTGYITGYGMNDV	(SEQ ID NO:2784)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I001A07	874	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I001A08	875	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I001A10	876	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I001A12	877	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I001B02	878	137-247	159-171	187-193	226-236	1-121	26-35	50-66	99-110	DRETKVGYGMDV (SEQ ID NO:2945)
I001B07	879	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I001C06	880	143-253	165-178	194-200	233-242	1-127	24-33	48-64	97-116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO:2158)
I001C08	881	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	EGSYDILTGYYVGVGRMDV (SEQ ID NO:2171)
I001C12	882	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I001D08	883	140-250	162-175	191-197	230-239	1-124	26-35	50-65	98-113	DSYDILTGVRGYFVDY (SEQ ID NO:2745)
I001D12	884	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I001E05	885	143-253	165-178	194-200	233-242	1-127	24-33	48-64	97-116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO:2158)
I001E07	886	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I001G09	887	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I001H05	888	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	ERHYDILTGYYTGYGMDV (SEQ ID NO:2784)
I001H08	889	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I003A01	890	141-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO:2852)
I003A06	891	141-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO:2852)
I003A07	892	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	DGYDILTGYSYVGMDV (SEQ ID NO:2135)
I003A10	893	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDY (SEQ ID NO:2179)
I003B03	894	141-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO:2852)
I003B04	895	140-248	162-172	188-194	227-237	1-122	25-34	49-65	98-111	RYGDPFYYYYYMN (SEQ ID NO:2755)
I003B09	896	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	DGYDILTGYSYVGMDV (SEQ ID NO:2135)
I003C01	897	142-252	164-176	192-198	231-241	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I003C02	898	142-252	164-176	192-198	231-241	1-125	26-35	50-66	99-114	GDYDILTGYPACFCQI (SEQ ID NO:2854)
I003C03	899	142-250	164-174	190-196	229-239	1-125	26-35	50-66	99-114	GDYDILTGYPACFCQI (SEQ ID NO:2854)
I003C12	900	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDY (SEQ ID NO:2179)
I003D04	901	140-250	162-174	190-196	229-239	1-123	26-35	50-66	99-112	RYGDPFYYYYYMN (SEQ ID NO:2755)
I003E05	902	142-253	164-176	192-198	231-242	1-125	26-35	50-66	99-114	GDYDILTGYPACFCQI (SEQ ID NO:2854)
I003F01	903	141-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO:2852)
I003F02	904	140-251	162-175	191-197	230-240	1-123	26-35	50-66	99-112	RYGDPFYYYYYMN (SEQ ID NO:2755)
I003G01	905	145-254	168-179	195-201	234-243	1-127	26-35	50-66	99-116	GTGYDILTGYYMGSAFDQ (SEQ ID NO:2800)
I003G05	906	144-255	166-179	195-201	234-244	1-127	26-35	50-66	99-116	GSYDILTGYYTGSPLDY (SEQ ID NO:2766)
I003G06	907	146-256	168-181	197-203	236-245	1-129	26-35	50-66	99-118	DRGGNYDILTGYYFHHGVDV (SEQ ID NO:2914)
I003G11	908	144-251	165-175	191-197	230-240	1-128	26-35	50-66	99-117	DAQSYDILTGYYQSYAFDI (SEQ ID NO:2183)
I003H02	909	142-253	164-176	192-198	233-242	1-124	26-35	50-66	99-113	DNYDILTGYSRRFDP (SEQ ID NO:2942)
I003H05	910	141-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO:2852)
I003H08	911	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	DGYDILTGYSYVGMDV (SEQ ID NO:2135)
I005A01	912	141-249	162-172	188-194	227-238	1-125	26-35	50-66	99-114	SHYDILTGLNYWYFDL (SEQ ID NO:2166)
I005A02	913	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	EGRDILTGYYVYGLDV (SEQ ID NO:2893)
I005B01	914	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	SHYDILTGLNYWYFDL (SEQ ID NO:2166)
I005B09	915	137-247	159-172	188-194	227-236	1-121	26-35	50-65	98-110	TYDILTGRFFDI (SEQ ID NO:2866)
I005C01	916	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	SHYDILTGLNYWYFDL (SEQ ID NO:2166)
I005D02	917	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	DLRYDILTGYYHDAFDI (SEQ ID NO:2890)
I005D03	918	142-249	165-175	191-197	230-238	1-126	26-35	50-66	99-115	GAYYDILTGYYPYGMDV (SEQ ID NO:2860)
I005E01	919	142-249	165-175	191-197	230-238	1-126	26-35	50-66	99-115	GTYYDILTGYYPHYGMDV (SEQ ID NO:2774)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I005E08	920	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 SHYDILTGLNYYWFDL	(SEQ ID NO:2166)
I005F01	921	142-248	164-174	190-196	229-238	1-124	26-35	50-66	99-113 DQHDILTGYYVGM DV	(SEQ ID NO:2921)
I005F02	922	144-251	167-177	193-199	232-240	1-128	26-35	50-66	99-117 VSPSYDILTGYYLPHAFDV	(SEQ ID NO:2849)
I005F04	923	137-247	159-172	188-194	227-236	1-121	26-35	50-65	98-110 TTYDILTGRRFDI	(SEQ ID NO:2866)
I005F08	924	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113 PSYDILTGYYLYFDY	(SEQ ID NO:2850)
I005G01	925	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 DLRYDILTGHDADFID	(SEQ ID NO:2890)
I005G08	926	142-249	165-175	191-197	230-238	1-126	26-35	50-66	99-115 GAYDILTGYYPYGMDV	(SEQ ID NO:2860)
I005H02	927	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113 GQYDILTGYNWFDP	(SEQ ID NO:2857)
I006B01	928	139-246	160-170	186-192	225-235	1-123	26-35	50-66	99-112 SRDLLLPHYGMDV	(SEQ ID NO:2133)
I006C09	929	143-253	165-177	193-199	232-242	1-127	26-35	50-66	99-116 GGYSSGWLRCGPYNWFDP	(SEQ ID NO:2967)
I006D09	930	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 GDYDILTGYYIPLRDY	(SEQ ID NO:2792)
I006E01	931	143-253	165-178	194-200	233-242	1-127	26-35	50-68	101-116 NLPDVTWLPYYMYMDV	(SEQ ID NO:2965)
I006E07	932	143-250	166-176	192-198	231-239	1-127	26-35	50-66	99-116 ADYDILTGYSPLTYGMDV	(SEQ ID NO:2762)
I006F01	933	140-250	162-175	191-197	230-239	1-124	26-35	50-68	101-113 MYDILTGHNEDY	(SEQ ID NO:2879)
I006F02	934	142-253	164-176	192-198	231-242	1-126	26-35	50-66	99-115 VSRDILTGNYYYGMDV	(SEQ ID NO:2817)
I006F07	935	143-253	165-177	193-199	232-242	1-127	26-35	50-66	99-116 GGYSSGWLRCGPYNWFDP	(SEQ ID NO:2967)
I006G01	936	146-253	169-179	195-201	234-242	1-130	26-35	50-68	101-119 AGGYDILTGDRYYYYGMDV	(SEQ ID NO:2877)
I006G04	937	132-239	153-163	179-185	218-228	1-116	26-35	50-66	99-105 RRYALDY	(SEQ ID NO:2920)
I006H01	938	146-253	167-177	193-199	232-242	1-130	26-35	50-65	98-119 DRGSYDILTGYYTPPHYYGMDV	(SEQ ID NO:2761)
I006H02	939	143-253	165-177	193-199	232-242	1-127	26-35	50-66	99-116 GGYSSGWLRCGPYNWFDP	(SEQ ID NO:2967)
I007A01	940	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I007A08	941	139-249	161-174	190-196	229-238	1-123	26-35	50-66	99-114 SHYDILTGLNYYWFDY	(SEQ ID NO:2746)
I007A11	942	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113 ENYDPLTGYYGAFDI	(SEQ ID NO:2772)
I007A12	943	144-251	165-175	191-197	230-240	1-128	26-35	50-68	101-117 GIYDILTGYNHWDGAFDI	(SEQ ID NO:2892)
I007B04	944	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I007C04	945	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I007C08	946	142-249	163-173	189-195	228-238	1-126	26-35	50-65	98-115 IRLYCYSLTGYYPYGMDD	(SEQ ID NO:2810)
I007C12	947	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113 TNYDILTGYYQGV DY	(SEQ ID NO:2782)
I007D07	948	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113 GQYDILTGYNWFDP	(SEQ ID NO:2857)
I007D08	949	144-251	165-175	191-197	230-240	1-128	26-35	50-68	101-117 GIYDILTGYNHWDGAFDI	(SEQ ID NO:2872)
I007E03	950	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I007E10	951	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 DFYDILTGYPGGM DV	(SEQ ID NO:2741)
I007E11	952	144-251	165-175	191-197	230-240	1-128	26-35	50-66	99-117 DLPYDILTGYSLSGMDV	(SEQ ID NO:2923)
I007F06	953	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I007F08	954	143-253	165-178	194-200	233-242	1-127	26-35	50-65	98-116 GRRYDILTGYYHHGMDV	(SEQ ID NO:2811)
I007G07	955	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 SHYDILTGLNYYWFDL	(SEQ ID NO:2166)
I007G09	956	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115 DSGGDILTGYYMPYFDY	(SEQ ID NO:2847)
I007G10	957	142-249	163-173	189-195	228-238	1-126	26-35	50-65	98-115 VGLYYDILTGYYPSGMDV	(SEQ ID NO:2805)
I007H07	958	147-257	169-182	198-204	237-246	1-131	26-35	50-68	101-120 SQAHYDILTGYYLWSYGM DV	(SEQ ID NO:2875)
I007H11	959	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 ESYDILTGYYRHYGMDL	(SEQ ID NO:2891)
I008A02	960	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I008A05	961	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I008A06	962	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I008A07	963	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115 DREYDLLTGYYLHAFDM	(SEQ ID NO:2960)
I008A12	964	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113 ENYDPLTGYYGAFDI	(SEQ ID NO:2772)
I008B02	965	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I008B04	966	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116 DGSYDILTGYIIDNYMDV	(SEQ ID NO:2154)
I008B05	967	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 DHYDILTGLYYYGMDV	(SEQ ID NO:2760)
I008B06	968	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I008B07	969	140-247	163-173	189-195	228-236	1-124	24-33	48-64	97-113 GRRYDILTGYKGPLDY	(SEQ ID NO:2902)
I008B10	970	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 AYYDNLTGFLPYGMGV	(SEQ ID NO:2947)
I008B11	971	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117 EGYDILTGYFLDYHGMVDV	(SEQ ID NO:2753)
I008C06	972	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I008C08	973	149-259	171-183	199-205	238-248	1-133	26-35	50-66	99-122 GPRGGPYDILTGYVLSLSDAFDI	(SEQ ID NO:2729)
I008C09	974	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115 EYYDILTGYRDPYGMVDV	(SEQ ID NO:2973)
I008D01	975	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I008D02	976	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I008D03	977	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117 EVRNYDLLTRSYLAGPLDN	(SEQ ID NO:2751)
I008D04	978	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I008D05	979	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I008D06	980	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I008D07	981	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117 DRGYDILTGYRGGHGMVDV	(SEQ ID NO:2837)
I008D08	982	144-251	165-175	191-197	230-240	1-128	26-35	50-66	99-117 DLPYYDILTGYSLTSGMDV	(SEQ ID NO:2923)
I008D12	983	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117 EEGFYDILTGYYPGYFDY	(SEQ ID NO:2974)
I008E01	984	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I008E02	985	137-247	159-172	188-194	227-236	1-121	20-31	46-63	96-110 EGYDILTGYSKFLDY	(SEQ ID NO:2906)
I008E03	986	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I008E04	987	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I008E08	988	141-252	163-175	191-197	230-241	1-125	26-35	50-66	99-114 SHYDILTGLNYYWYFDL	(SEQ ID NO:2166)
I008E09	989	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116 ERADYDILTGYFYDMDV	(SEQ ID NO:2833)
I008E12	990	141-251	163-176	192-198	231-240	1-125	26-37	52-67	100-114 FRYDILTSYYGMDV	(SEQ ID NO:2734)
I008F03	991	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I008F06	992	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I008F07	993	143-250	164-174	190-196	229-239	1-127	26-35	50-65	98-116 GRRYDILTGYVYHGMVDV	(SEQ ID NO:2811)
I008F08	994	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116 GHYDILTGYDDYYGMDV	(SEQ ID NO:2844)
I008F09	995	133-243	155-168	184-190	223-232	1-117	26-35	50-65	98-106 HDILTGFDY	(SEQ ID NO:2904)
I008F10	996	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113 SGYDILTGVLYGMDV	(SEQ ID NO:2934)
I008F11	997	144-251	165-175	191-197	230-240	1-128	26-35	50-68	101-117 APYDILTGYSDYYGMDV	(SEQ ID NO:2968)
I008G02	998	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I008G03	999	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113 GDYDPLTGYSFGVDV	(SEQ ID NO:2941)
I008G04	1000	143-253	165-178	194-200	233-242	1-127	26-35	50-65	98-116 EGSYDILTGYVVGVRMDV	(SEQ ID NO:2171)
I008G05	1001	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117 DGYDILTGGFYYGMDV	(SEQ ID NO:2899)
I008G11	1002	136-246	158-171	187-193	226-235	1-120	26-35	50-66	99-109 AYYDILTGLDY	(SEQ ID NO:2966)
I008G12	1003	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116 DQYDILTGYVHYGMDV	(SEQ ID NO:2964)
I008H02	1004	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114 DQVLLMDHNYMDV	(SEQ ID NO:2918)
I008H03	1005	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I008H06	1006	143-253	165-178	194-200	233-242	1-127	26-35	50-65	98-116 EGSYDILTGYVVGVRMDV	(SEQ ID NO:2171)
I008H09	1007	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116 DQYDILTGYVHYGMDV	(SEQ ID NO:2964)
I008H11	1008	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114 TKYDILTGYVYMDV	(SEQ ID NO:2856)
I012B03	1009	141-249	163-175	191-197	230-238	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I012B06	1010	141-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I012B10	1011	141-251	163-175	191-197	230-240	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I012C03	1012	143-255	165-178	194-200	233-244	1-126	26-35	50-66	99-115 TDRFGAKDVTSRWGMDV	(SEQ ID NO:2814)
I012C06	1013	141-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I012C09	1014	142-250	164-174	190-196	229-239	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I012D12	1015	146-256	168-180	196-202	235-245	1-129	26-35	50-66	99-118 DRGNYDILTGYYFHHGVVDV	(SEQ ID NO:2914)
I012E07	1016	142-252	164-176	192-198	231-241	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I012E08	1017	140-250	162-174	190-196	229-239	1-123	26-35	50-66	99-112 RYGDPPFYMYMNV	(SEQ ID NO:2755)
I012E09	1018	141-247	163-173	189-195	228-236	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I012F05	1019	141-249	163-173	189-195	228-238	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I012F12	1020	142-251	164-176	192-198	231-240	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I012G03	1021	142-252	164-176	192-198	231-241	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I012G05	1022	141-250	163-173	189-195	228-239	1-123	26-35	50-66	99-112 RYGDPPFYMYMNV	(SEQ ID NO:2755)
I012G10	1023	140-251	162-175	191-197	230-240	1-123	26-35	50-66	99-112 RYGDPPFYMYMNV	(SEQ ID NO:2755)
I012H09	1024	141-249	163-173	189-195	228-238	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I013A10	1025	148-259	170-182	198-204	237-248	1-131	26-35	50-66	99-120 SSPPKWDALTGHSYHSAMDV	(SEQ ID NO:2159)
I013A12	1026	149-256	171-181	197-203	236-245	1-131	26-35	50-66	99-120 SSPPKWDALTGHSYHSAMDV	(SEQ ID NO:2159)
I013B04	1027	149-256	172-182	198-204	237-245	1-131	26-35	50-66	99-120 SSPPKWDALTGDSYHSAMDV	(SEQ ID NO:2165)
I013B09	1028	149-257	171-181	197-203	236-246	1-131	26-35	50-66	99-120 SSPPKWDALTGHSYHSAMDV	(SEQ ID NO:2159)
I013C02	1029	148-258	170-182	198-204	237-247	1-131	26-35	50-66	99-120 SSPPKWDALTGDSYHSAMDV	(SEQ ID NO:2818)
I013C04	1030	139-249	161-173	189-195	228-238	1-121	26-35	50-66	99-110 GYDSSAFRAFDI	(SEQ ID NO:2136)
I013D02	1031	138-248	160-173	189-195	228-237	1-121	26-35	50-66	99-110 GYDSSAFRAFDI	(SEQ ID NO:2136)
I013D03	1032	148-259	170-183	199-205	238-248	1-131	26-35	50-66	99-120 SSPPKWDALTGDSYHSAMDV	(SEQ ID NO:2165)
I013D10	1033	146-257	168-181	197-203	236-246	1-129	26-35	50-66	99-118 GLRHVTLPGTGRGHFYMDV	(SEQ ID NO:2789)
I013E02	1034	148-259	170-183	199-205	238-248	1-131	26-35	50-66	99-120 GREDTDKVKPMDRYHHYYMDV	(SEQ ID NO:2809)
I013E05	1035	139-249	162-173	189-195	228-238	1-121	26-35	50-66	99-110 GYDSSAFRAFDI	(SEQ ID NO:2136)
I013E09	1036	148-260	170-183	199-205	238-249	1-131	26-35	50-66	99-120 SSPPKWDALTGDSYHSAMDV	(SEQ ID NO:2165)
I013F03	1037	138-248	160-172	188-194	227-237	1-121	26-35	50-66	99-110 GYDSSAFRAFDI	(SEQ ID NO:2136)
I013F04	1038	148-258	170-182	198-204	237-247	1-131	26-35	50-66	99-120 SSPPKWDALTGHSYHSAMDV	(SEQ ID NO:2159)
I013F07	1039	147-260	170-185	201-207	240-249	1-129	26-35	50-66	99-118 AATTSQKHKNYAYIFYGMDV	(SEQ ID NO:2131)
I013F09	1040	138-248	160-172	188-194	227-237	1-121	26-35	50-66	99-110 GYDSSAFRAFDI	(SEQ ID NO:2136)
I013F10	1041	148-259	170-183	199-205	238-248	1-131	26-35	50-66	99-120 SSPPKWDALTGHSYHSAMDV	(SEQ ID NO:2159)
I013H04	1042	148-258	170-182	198-204	237-247	1-131	26-35	50-66	99-120 SSPPKWDALTGHSYHSAMDV	(SEQ ID NO:2159)
I013H07	1043	148-259	170-183	199-205	238-248	1-131	26-35	50-66	99-120 GREDTDKVKPMDRYHHYYMDV	(SEQ ID NO:2809)
I014A12	1044	143-253	165-178	194-200	233-242	1-127	24-33	48-64	97-116 EGGNYDILTGYYIGNGAFDI	(SEQ ID NO:2158)
I014C06	1045	142-254	164-177	193-200	233-243	1-125	26-35	50-66	99-114 GDYDILTGYPACFCQI	(SEQ ID NO:2854)
I014C10	1046	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I014C12	1047	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I014E06	1048	142-252	164-176	192-198	231-241	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I014F02	1049	143-251	166-176	192-198	231-240	1-125	26-37	52-67	100-114 AGYDLLTGYPFYFDS	(SEQ ID NO:2757)
I016A08	1050	144-251	165-175	191-197	230-240	1-128	26-35	50-66	99-117 EVRNYDLLTRSYLAGPLDN	(SEQ ID NO:2751)
I016A09	1051	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I016C02	1052	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I016C03	1053	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I016C05	1054	148-255	169-179	195-201	234-244	1-132	26-35	50-66	99-121 VQMDSEYDILLTGINVGPPYFDY	(SEQ ID NO:2132)
I016C09	1055	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I016C11	1056	148-255	169-179	195-201	234-244	1-132	26-35	50-66	99-121 VQMDSEYDILLTGINVGPPYFDY	(SEQ ID NO:2132)
I016D10	1057	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I016D11	1058	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I016E03	1059	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I016E04	1060	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I016F03	1061	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I016F11	1062	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I016G01	1063	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I016G06	1064	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I016G12	1065	148-255	169-179	195-201	234-244	1-132	26-35	50-66	99-121	VQMDSEYDILLTGINVGPPYFDY (SEQ ID NO:2132)
I016H10	1066	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I017A06	1067	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I017A07	1068	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I017A11	1069	140-253	162-175	191-197	233-242	1-124	25-34	49-65	98-113	ATYDPLTGYSFDGLDI (SEQ ID NO:2157)
I017E12	1070	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I017G03	1071	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I017G07	1072	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I017H01	1073	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I018A02	1074	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I018A04	1075	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	EGSYDILTGYYVGVGRMDV (SEQ ID NO:2171)
I018A05	1076	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I018A11	1077	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I018B02	1078	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I018B08	1079	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I018C04	1080	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I018D02	1081	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I018E06	1082	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I018E08	1083	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I018F04	1084	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I018G06	1085	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I018H07	1086	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I019E05	1087	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	ERHYVDILTGYSQTYGMDV (SEQ ID NO:2784)
I019F06	1088	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	ERHYVDILTGYSQTYGMDV (SEQ ID NO:2784)
I019G12	1089	143-253	165-178	194-200	233-242	1-127	24-33	48-64	97-116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO:2158)
I020D01	1090	137-247	159-171	187-193	226-236	1-121	26-35	50-66	99-110	DRETKIVGYGMDV (SEQ ID NO:2945)
I020D05	1091	143-253	165-178	194-200	233-242	1-127	24-33	48-64	97-116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO:2158)
I020E10	1092	143-253	165-178	194-200	233-242	1-127	24-33	48-64	97-116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO:2158)
I020G12	1093	143-253	165-178	194-200	233-242	1-127	24-33	48-64	97-116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO:2158)
I020H06	1094	143-253	165-178	194-200	233-242	1-127	24-33	48-64	97-116	EGGNYHILTGYYIGNGAFDI (SEQ ID NO:2896)
I020H10	1095	143-253	165-178	194-200	233-242	1-127	24-33	48-64	97-116	EGENYDILTGYYIGNGAFDI (SEQ ID NO:2903)
I021A11	1096	143-253	165-178	194-200	233-242	1-127	24-33	48-64	97-116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO:2158)
I021B01	1097	143-253	165-178	194-200	233-242	1-127	24-33	48-64	97-116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO:2158)
I021C11	1098	143-253	165-178	194-200	233-242	1-127	24-33	48-64	97-116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO:2158)
I021D12	1099	137-247	159-171	187-193	226-236	1-121	26-35	50-66	99-110	DRETKVGYGMDV (SEQ ID NO:2945)
I021E10	1100	143-253	165-178	194-200	233-242	1-127	24-33	48-64	97-116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO:2158)
I021G02	1101	143-253	165-178	194-200	233-242	1-127	24-33	48-64	97-116	EGGNYDILTGYYIGNGAFDI (SEQ ID NO:2158)
I022A08	1102	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	DGYYDILTGYSYGGMDV (SEQ ID NO:2135)
I022B01	1103	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I022B10	1104	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	MEYDILTGYGKYFDY (SEQ ID NO:2179)
I022C02	1105	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	DGYDILTGYSYGMDV (SEQ ID NO:2135)
I022C04	1106	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I022C08	1107	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I022D06	1108	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	DGYDILTGYSYGMDV (SEQ ID NO:2135)
I022E08	1109	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	ASYDILTGYKGFDFI (SEQ ID NO:2855)
I022F01	1110	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	DGYDILTGYSYGMDV (SEQ ID NO:2135)
I022F04	1111	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	DGYDILTGYSYGMDV (SEQ ID NO:2135)
I022F12	1112	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113	GDYDILTGYTYYIDV (SEQ ID NO:2859)
I022G11	1113	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	DGYDILTGYSYGMDV (SEQ ID NO:2135)
I023D01	1114	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	SHYDILTGLNWFYFDL (SEQ ID NO:2166)
I023D04	1115	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	DGYDILTGYSYGMDV (SEQ ID NO:2135)
I024B04	1116	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113	VYDILTGYNLFDFY (SEQ ID NO:2177)
I024D01	1117	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	DGYDILTGYSYGMDV (SEQ ID NO:2135)
I024F06	1118	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	DGYDILTGYSYGMDV (SEQ ID NO:2135)
I024H01	1119	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	DGYDILTGYSYGMDV (SEQ ID NO:2135)
I024H07	1120	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	DGYDILTGYSYGMDV (SEQ ID NO:2135)
I025A01	1121	141-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO:2852)
I025A04	1122	141-251	163-175	191-197	230-240	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I025A07	1123	141-249	163-173	189-195	228-238	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I025B01	1124	134-244	156-168	184-190	223-233	1-117	26-35	50-66	99-106	DQGRYLDL (SEQ ID NO:2175)
I025B10	1125	142-253	164-176	192-198	233-242	1-124	26-35	50-66	99-113	DNYDILTGYSRFFDP (SEQ ID NO:2942)
I025B12	1126	141-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO:2852)
I025C07	1127	141-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO:2852)
I025D11	1128	142-252	164-176	192-198	231-241	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I025E04	1129	142-252	164-176	192-198	231-241	1-126	26-35	50-66	99-115	PLGITAVRGAKTDAFGI (SEQ ID NO:2929)
I025E05	1130	141-251	163-175	191-197	230-240	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I025E07	1131	142-252	164-176	192-198	231-241	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I025E10	1132	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I025F01	1133	140-251	162-175	191-197	230-240	1-123	26-35	50-66	99-112	RYGDPFYYYMMNV (SEQ ID NO:2755)
I025F08	1134	138-248	160-172	188-194	227-237	1-121	26-35	50-66	99-110	GCSSQNFYGMVDV (SEQ ID NO:2884)
I025G03	1135	142-252	164-176	192-198	231-241	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I025G08	1136	141-254	163-176	192-198	231-243	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I025H02	1137	145-255	167-179	195-201	234-244	1-128	26-35	50-65	98-117	AGSGFHDILTGYKGYFDY (SEQ ID NO:2961)
I026A01	1138	143-249	165-175	191-197	230-238	1-125	26-35	50-66	99-114	GDYDILTGYPARCFQI (SEQ ID NO:2854)
I026B01	1139	144-254	166-178	194-200	233-243	1-127	26-35	50-66	99-116	GSVDILTGYTKSGMGV (SEQ ID NO:2733)
I026B06	1140	141-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO:2852)
I026C06	1141	141-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO:2852)
I026C10	1142	139-249	161-174	190-196	229-238	1-122	26-34	49-65	98-111	RYGDPFYYYMMNV (SEQ ID NO:2755)
I026C11	1143	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I026D09	1144	140-252	162-175	191-197	230-241	1-123	26-35	50-66	99-112	RYGDPFYYYMMNV (SEQ ID NO:2755)
I026E04	1145	142-252	164-176	192-198	231-241	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I026E06	1146	141-251	163-175	191-197	230-240	1-124	26-35	50-66	99-113	GYDDILTGYIMALDY (SEQ ID NO:2821)
I026E09	1147	141-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO:2852)
I026F01	1148	141-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO:2852)
I026F09	1149	141-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO:2852)

TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scPv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I026F12	1150	141-256	163-176	192-202	237-245	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO:2852)
I026G08	1151	141-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO:2852)
I026G10	1152	141-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO:2852)
I026G11	1153	144-255	166-179	195-201	234-244	1-127	26-35	50-66	99-116	GTGYDILTGYMGSAPDQ (SEQ ID NO:2800)
I026H02	1154	140-251	162-175	191-197	230-240	1-123	26-35	50-66	99-112	RYGDPFYYYYYMN (SEQ ID NO:2755)
I026H06	1155	141-251	163-175	191-197	230-240	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I026H10	1156	145-255	167-179	195-201	234-244	1-128	26-35	50-66	99-117	GGEYDILTGYFGLGVYDY (SEQ ID NO:2170)
I027A09	1157	141-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO:2852)
I027B02	1158	140-250	162-174	190-196	229-239	1-123	26-35	50-66	99-112	RYGDPFYYYYYMN (SEQ ID NO:2755)
I027B05	1159	141-250	163-176	192-198	230-239	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO:2852)
I027C08	1160	139-249	161-174	190-196	229-238	1-122	26-34	49-63	96-111	ELGSSIVGATTGALDM (SEQ ID NO:2852)
I027D02	1161	142-250	164-174	190-196	229-239	1-125	26-35	50-66	99-114	DPFGAVPGYYYAMDV (SEQ ID NO:2826)
I027E03	1162	141-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO:2852)
I027E05	1163	142-252	164-176	192-198	231-241	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I027F04	1164	145-252	167-176	192-198	231-241	1-128	26-35	50-66	99-117	GPWYDPLFPSPGRHYGLDV (SEQ ID NO:2793)
I027F05	1165	141-254	163-176	192-198	231-243	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I027F11	1166	141-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO:2852)
I027G06	1167	142-253	164-176	192-198	233-242	1-124	26-35	50-66	99-113	DNYDILTGYSRRFDP (SEQ ID NO:2942)
I027G07	1168	142-250	164-174	190-196	229-239	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I027H03	1169	142-252	164-176	192-198	231-241	1-125	26-35	50-66	99-114	GDYDILTGYPACFCQI (SEQ ID NO:2854)
I028A04	1170	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116	DMYDILTGYTGLAFDM (SEQ ID NO:2880)
I028A07	1171	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	VLNYDILTGYTGMVDV (SEQ ID NO:2832)
I028B08	1172	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I028B10	1173	148-258	170-183	199-205	238-247	1-132	26-35	50-68	101-121	DFGYDILTGYIGAFYAFDI (SEQ ID NO:2861)
I028C01	1174	142-250	165-175	191-197	230-239	1-126	26-37	52-69	102-115	GGHTCIPTCHNGG (SEQ ID NO:2796)
I028C04	1175	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116	DMYDILTGYTGLAFDM (SEQ ID NO:2880)
I028C08	1176	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I028D04	1177	140-247	163-173	189-195	228-236	1-124	26-35	50-65	98-113	ATQDILTGVLVSGMDV (SEQ ID NO:2977)
I028D05	1178	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	EHYDILTGYSLLGMDV (SEQ ID NO:2907)
I028D12	1179	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116	DGYDILTGYSVYVGMVDV (SEQ ID NO:2938)
I028E06	1180	143-253	165-178	194-200	233-242	1-127	26-35	50-65	98-116	EGSYDILTGYVVGVRMDV (SEQ ID NO:2171)
I028E07	1181	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I028E08	1182	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I028F06	1183	146-256	168-180	196-202	235-245	1-130	26-35	50-66	99-119	DDRRGYDILTGYYRFGSFDI (SEQ ID NO:2901)
I028F08	1184	134-244	156-169	185-191	224-233	1-118	26-35	50-66	99-107	DIDIGGDDS (SEQ ID NO:2954)
I028G08	1185	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	VSGYNSGYFESYDMVDV (SEQ ID NO:2732)
I028G09	1186	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	EVARNYDLLTRSYLAGPLDN (SEQ ID NO:2751)
I028G10	1187	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I028H02	1188	142-249	165-175	191-197	230-238	1-126	26-37	52-69	102-115	SGEPCITLACNLGG (SEQ ID NO:2797)
I028H03	1189	148-256	169-179	195-201	234-245	1-132	26-35	50-66	99-121	DASEYDILTGYLATGRNWFDP (SEQ ID NO:2888)
I028H06	1190	145-255	167-180	196-202	235-244	1-129	26-35	50-66	99-118	DPSPYDILTGYPLPYMDV (SEQ ID NO:2843)
I028H09	1191	140-250	162-175	191-197	230-239	1-124	26-35	50-68	101-113	EIDDILTGYMDV (SEQ ID NO:2905)
I029A10	1192	139-246	160-170	186-192	225-235	1-123	26-35	50-65	98-112	MNYDILTGLVNWFPD (SEQ ID NO:2786)
I029A12	1193	137-247	159-171	187-193	226-236	1-121	26-35	50-68	101-110	RDILTGFPYDS (SEQ ID NO:2933)
I029B11	1194	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I029C08	1195	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	EGSYDILTGYVVGVRMDV (SEQ ID NO:2171)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I029E10	1196	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117 EVRNYDLLTRSYLAGPLDN	(SEQ ID NO:2751)
I029F08	1197	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117 EVRNYDLLTRSYLAGPLDN	(SEQ ID NO:2751)
I029G08	1198	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 GYDILTGYSDFDI	(SEQ ID NO:2927)
I030A02	1199	143-253	165-177	193-199	232-242	1-126	26-35	50-66	99-115 TERFGAKDVTARWGMVDV	(SEQ ID NO:2874)
I030A03	1200	141-253	163-175	191-197	230-242	1-124	26-35	50-66	99-113 ENYDILTGYNFFDY	(SEQ ID NO:2737)
I030A04	1201	141-252	163-176	192-198	231-241	1-124	26-35	50-66	99-113 RQYDILTGYYGGFDY	(SEQ ID NO:2958)
I030A05	1202	141-249	163-175	191-197	230-238	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I030A09	1203	140-250	162-174	190-196	229-239	1-123	26-35	50-66	99-112 RYGDPPFYYYMMNV	(SEQ ID NO:2755)
I030A12	1204	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112 RYGDPPFYYYMMNV	(SEQ ID NO:2755)
I030B06	1205	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112 RYGDPPFYYYMMNV	(SEQ ID NO:2755)
I030B08	1206	141-247	163-173	189-195	228-236	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I030B10	1207	143-251	165-175	191-197	230-240	1-125	26-35	50-66	99-114 ELGHREGGYWSPYNV	(SEQ ID NO:2838)
I030C03	1208	140-252	162-175	191-197	230-241	1-123	26-35	50-66	99-112 RYGDPPFYYYMMNV	(SEQ ID NO:2755)
I030C06	1209	147-256	169-182	198-204	237-245	1-130	26-35	50-68	101-119 DPGNYDILTGYYYYGMDV	(SEQ ID NO:2935)
I030C08	1210	134-244	156-168	184-190	223-233	1-117	26-35	50-66	99-106 SGPGWFDP	(SEQ ID NO:2870)
I030C09	1211	141-251	163-175	191-197	230-240	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I030C10	1212	141-250	163-175	191-197	230-239	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I030C11	1213	140-251	162-175	191-197	230-240	1-123	26-35	50-66	99-112 RYGDPPFYYYMMNV	(SEQ ID NO:2755)
I030C12	1214	134-244	156-168	184-190	223-233	1-117	26-35	50-66	99-106 SGPGWFDP	(SEQ ID NO:2870)
I030D07	1215	141-249	163-173	189-195	228-238	1-123	26-35	50-66	99-112 RYGDPPFYYYMMNV	(SEQ ID NO:2755)
I030D12	1216	141-251	163-175	191-197	230-240	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I030E02	1217	140-251	162-175	191-197	230-240	1-123	26-35	50-66	99-112 RYGDPPFYYYMMNV	(SEQ ID NO:2755)
I030E05	1218	142-252	164-176	192-198	231-241	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I030E07	1219	142-251	165-176	192-198	231-240	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I030E08	1220	141-251	163-175	191-197	230-240	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I030E09	1221	141-252	163-176	192-198	231-241	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I030E10	1222	140-250	162-174	190-196	229-239	1-123	26-35	50-66	99-112 RYGDPPFYYYMMNV	(SEQ ID NO:2755)
I030F02	1223	142-252	164-176	192-198	231-241	1-125	26-37	52-67	100-114 AGYDLLTGYPFYFDS	(SEQ ID NO:2757)
I030F05	1224	141-251	163-175	191-197	230-240	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I030F06	1225	140-251	162-175	191-197	230-240	1-123	26-35	50-66	99-112 RYGDPPFYYYMMNV	(SEQ ID NO:2755)
I030F08	1226	141-254	163-176	192-198	231-243	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I030F09	1227	142-253	164-176	192-198	231-242	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I030F11	1228	140-250	162-174	190-196	229-239	1-123	26-35	50-66	99-112 RYGDPPFYYYMMNV	(SEQ ID NO:2755)
I030F12	1229	141-251	163-175	191-197	230-240	1-124	26-35	50-66	99-113 DNYDILTGYSRRFDP	(SEQ ID NO:2942)
I030G03	1230	141-256	163-176	192-202	237-245	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I030G07	1231	140-251	162-175	191-197	230-240	1-123	26-35	50-66	99-112 RYGDPPFYYYMMNV	(SEQ ID NO:2755)
I030G09	1232	142-251	164-174	190-196	229-240	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I030H05	1233	146-255	168-181	197-203	236-244	1-129	26-35	50-66	99-118 DRGNYDILTGYYFHHGVDV	(SEQ ID NO:2914)
I030H06	1234	148-258	170-182	198-204	239-247	1-130	26-37	52-69	102-119 ATKSYDILTRMYHHMDV	(SEQ ID NO:2748)
I030H10	1235	141-253	163-176	192-198	231-242	1-124	26-35	50-66	99-113 DNYDILTGYSRRFDP	(SEQ ID NO:2942)
I030H11	1236	142-252	164-176	192-198	231-241	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I031A01	1237	138-248	160-173	189-195	228-237	1-121	26-35	50-66	99-110 GYDSSAFRAFDI	(SEQ ID NO:2136)
I031A03	1238	143-251	166-176	192-198	231-240	1-125	26-35	50-66	99-114 PYYDPLTAYTFQYFCN	(SEQ ID NO:2806)
I031A08	1239	148-258	170-182	198-204	237-247	1-131	26-35	50-66	99-120 GREDTDKVKPMDRYHHYMDV	(SEQ ID NO:2809)
I031A12	1240	147-257	169-181	197-203	236-246	1-130	26-35	50-66	99-119 GREDTDKVKPMDRYHHYMDV	(SEQ ID NO:2972)
I031B03	1241	137-246	159-172	188-194	227-235	1-120	26-35	50-68	101-109 GLGHTSDSDS	(SEQ ID NO:2959)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I031B06	1242	143-253	165-177	193-199	232-242	1-126	26-35	50-66	99-115 AKGYYYDSSGASDVFDV	(SEQ ID NO:2871)
I031B07	1243	148-258	170-182	198-204	237-247	1-131	26-35	50-66	99-120 GREDTDKVKPWRYYHYHYMDV	(SEQ ID NO:2809)
I031B08	1244	149-260	171-183	199-205	238-249	1-131	26-35	50-66	99-120 SSPPKWDALTGHSYHSAMDV	(SEQ ID NO:2159)
I031B09	1245	148-258	170-182	198-204	237-247	1-131	26-35	50-66	99-120 SNPPKWDALTGHSYHSAMDV	(SEQ ID NO:2840)
I031B11	1246	138-248	160-172	188-194	227-237	1-121	26-35	50-66	99-110 GYDSSAFRAFDI	(SEQ ID NO:2136)
I031B12	1247	148-259	170-183	199-205	238-248	1-131	26-35	50-66	99-120 GREDTDKVKPWRYYHYHYMDV	(SEQ ID NO:2809)
I031C01	1248	138-248	160-172	188-194	227-237	1-121	26-35	50-66	99-110 GYDSSAFRAFDI	(SEQ ID NO:2136)
I031C02	1249	142-253	164-177	193-199	232-242	1-125	26-35	50-66	99-114 PFYDTLTSYVFQYFDH	(SEQ ID NO:2137)
I031C04	1250	149-260	171-183	199-205	238-249	1-131	26-35	50-66	99-120 GRKOTDKVKPWRYYHYHYMDV	(SEQ ID NO:2813)
I031C08	1251	139-248	161-171	187-193	226-237	1-121	26-35	50-66	99-110 GYDSSAFRAFDI	(SEQ ID NO:2136)
I031C11	1252	149-257	171-181	197-203	236-246	1-131	26-35	50-66	99-120 GREDTDKVKPWRYYHYHYMDV	(SEQ ID NO:2809)
I031D01	1253	146-256	168-180	196-202	235-245	1-129	26-35	50-66	99-118 AATTSQKHNYAYFFYGMV	(SEQ ID NO:2131)
I031D04	1254	138-248	160-172	188-194	227-237	1-121	26-35	50-66	99-110 GYDSSAFRAFDI	(SEQ ID NO:2136)
I031D06	1255	148-258	170-182	198-204	237-247	1-131	26-35	50-66	99-120 GREDTDKVKLWDRYYHYHYMDV	(SEQ ID NO:2807)
I031D08	1256	145-257	167-180	196-202	235-246	1-128	26-35	50-66	99-117 VRPKLRYFDWLSRHDAFDL	(SEQ ID NO:2820)
I031D09	1257	139-247	161-171	187-193	226-236	1-121	26-35	50-66	99-110 GYDSSAFRAFDI	(SEQ ID NO:2136)
I031D11	1258	149-256	171-181	197-203	236-245	1-131	26-35	50-66	99-120 SSPPKWDALTGSSYHSAMDV	(SEQ ID NO:2165)
I031D12	1259	146-254	168-178	194-200	233-243	1-128	26-35	50-66	99-117 DKAHGEYGRDYYYYYGMV	(SEQ ID NO:2735)
I031E01	1260	148-258	170-182	198-204	237-247	1-131	26-35	50-66	99-120 SSPPKWDALTGHSYHSAMDV	(SEQ ID NO:2159)
I031E05	1261	149-257	171-181	197-203	236-246	1-131	26-35	50-66	99-120 SGPPKWDALTGHSYHSAMDV	(SEQ ID NO:2848)
I031E07	1262	148-259	170-182	198-204	237-248	1-131	26-35	50-66	99-120 SSPPKWDALTGHSYHSAMDV	(SEQ ID NO:2159)
I031E08	1263	148-259	170-183	199-205	238-248	1-131	26-35	50-66	99-120 GREDTDKVKPWRYYHYHYMDV	(SEQ ID NO:2809)
I031E09	1264	139-246	162-173	189-195	228-235	1-121	26-35	50-66	99-110 GYDSSAFRAFDI	(SEQ ID NO:2136)
I031E10	1265	148-258	170-182	198-204	237-247	1-131	26-35	50-66	99-120 SSPPKWDALTGSSYHSAMDV	(SEQ ID NO:2165)
I031E11	1266	148-258	170-182	198-204	237-247	1-131	26-35	50-66	99-120 SSPPKWDALTGHSYHSAMDV	(SEQ ID NO:2159)
I031F01	1267	138-248	160-172	188-194	227-237	1-121	26-35	50-66	99-110 GYDSSAFRAFDI	(SEQ ID NO:2136)
I031F04	1268	139-246	162-172	188-194	227-235	1-121	26-35	50-66	99-110 GYDSSAFRAFDI	(SEQ ID NO:2136)
I031F06	1269	137-247	159-171	187-193	226-236	1-119	26-35	50-66	99-108 DTVRSGGMV	(SEQ ID NO:2804)
I031F10	1270	148-259	170-183	199-205	238-248	1-131	26-35	50-66	99-120 GREDTDKVKPWRYYHYHYMDV	(SEQ ID NO:2809)
I031F11	1271	145-255	167-179	195-201	234-244	1-128	26-35	50-66	99-117 DKAHGEYGRDYYYYYGMV	(SEQ ID NO:2735)
I031F12	1272	138-249	160-172	188-194	227-238	1-121	26-35	50-66	99-110 GYDSSAFRAFDI	(SEQ ID NO:2136)
I031G01	1273	138-248	160-172	188-194	227-237	1-121	26-35	50-66	99-110 GYDSSAFRAFDI	(SEQ ID NO:2136)
I031G03	1274	148-258	170-182	198-204	237-247	1-131	26-35	50-66	99-120 SSPPKWDALTGHSYHSAMDV	(SEQ ID NO:2159)
I031G05	1275	148-259	170-183	199-205	238-248	1-131	26-35	50-66	99-120 GREDTDKVKPWRYYHYHYMDV	(SEQ ID NO:2809)
I031G06	1276	148-258	170-182	198-204	237-247	1-131	26-35	50-66	99-120 GREDTDKVKPWRYYHYHYMDV	(SEQ ID NO:2809)
I031G07	1277	149-259	171-183	199-205	238-248	1-131	26-35	50-66	99-120 SSPPKWDALTGSSYHSAMDV	(SEQ ID NO:2816)
I031G09	1278	148-263	170-183	199-209	244-252	1-131	26-35	50-66	99-120 GREDTDKVKPWRYYHYHYMDV	(SEQ ID NO:2809)
I031G12	1279	146-256	168-180	196-202	235-245	1-129	26-35	50-66	99-118 AATTSQKHNYAYFFYGMV	(SEQ ID NO:2131)
I031H01	1280	138-250	160-173	189-195	228-239	1-121	26-35	50-66	99-110 GYDSSAFRAFDI	(SEQ ID NO:2136)
I031H02	1281	143-255	165-178	194-200	233-244	1-126	26-35	50-66	99-115 AKGYYYDSSGASDVFDV	(SEQ ID NO:2871)
I031H03	1282	148-260	170-183	199-205	238-249	1-131	26-35	50-66	99-120 GREDTDKVKPWRYYHYHYMDV	(SEQ ID NO:2809)
I031H06	1283	145-257	167-179	195-201	234-246	1-128	26-35	50-66	99-117 DKAHGEYGRDYYYYYGMV	(SEQ ID NO:2735)
I031H09	1284	145-255	167-179	195-201	234-244	1-128	26-35	50-66	99-117 DKAHGEYGRDYYYYYGMV	(SEQ ID NO:2735)
I031H10	1285	144-256	166-179	195-201	234-245	1-127	26-35	50-66	99-116 DRGTYGYDLVGGYYFDF	(SEQ ID NO:2931)
I031H11	1286	136-246	158-170	186-192	225-235	1-119	26-35	50-66	99-108 DTVRSGGMV	(SEQ ID NO:2804)
I033A08	1287	144-254	166-179	195-201	234-243	1-128	26-37	52-69	102-117 DRYDILTYGYYGYMDV	(SEQ ID NO:2129)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I033B11	1288	144-254	166-179	195-201	234-243	1-128	26-37	52-69	102-117 DRYDILTGYYTGMVDV	(SEQ ID NO:2129)
I033C01	1289	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117 EVRNYDLTSLYLAGPLDN	(SEQ ID NO:2751)
I033C08	1290	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115 EMGYDILTGYYLNYMDV	(SEQ ID NO:2862)
I033D02	1291	138-245	161-171	187-193	226-234	1-122	26-35	50-66	99-111 GDYDILTGYYMDV	(SEQ ID NO:2781)
I033D03	1292	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I033D05	1293	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I033D11	1294	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113 VKRDILTGYYVEGMDV	(SEQ ID NO:2869)
I033D12	1295	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117 GGPYDILTGYYMAVGFDI	(SEQ ID NO:2962)
I033E01	1296	139-249	161-173	189-195	228-238	1-123	26-35	50-66	99-112 DIDARLAALDAFDI	(SEQ ID NO:2794)
I033E06	1297	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATHDPLTGYSFDGFDI	(SEQ ID NO:2780)
I033E11	1298	143-253	165-177	193-199	232-242	1-127	26-35	50-66	99-116 HRSRSCSTSCRNDAPDI	(SEQ ID NO:2770)
I033E12	1299	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115 EMGYDILTGYYLNYMDV	(SEQ ID NO:2862)
I033F03	1300	139-246	160-170	186-192	225-235	1-123	26-35	50-66	99-112 EGAADYLNQYFQD	(SEQ ID NO:2768)
I033F08	1301	145-256	167-179	195-201	234-245	1-129	26-35	50-66	99-118 QKVYDILTGYYNYGMDV	(SEQ ID NO:2767)
I033F10	1302	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117 EVRNYDLTSLYLAGPLDN	(SEQ ID NO:2751)
I033F12	1303	134-241	155-165	181-187	220-230	1-118	26-35	50-66	99-107 DIDIGGDDS	(SEQ ID NO:2954)
I033G01	1304	143-253	165-178	194-200	233-242	1-127	24-33	48-64	97-116 EGGNYDILTGYYIGNAFDI	(SEQ ID NO:2158)
I033G03	1305	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115 PQGVTLVRAETDAFAI	(SEQ ID NO:2925)
I033G08	1306	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I033H04	1307	140-247	161-171	187-193	226-236	1-124	25-34	49-65	98-113 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I037A05	1308	139-246	160-170	186-192	225-235	1-123	26-35	50-66	99-112 SRDLLLPHYGMDV	(SEQ ID NO:2133)
I037B03	1309	141-251	163-175	191-197	230-240	1-125	26-35	50-66	99-114 SHYDILTRLNYYWFDL	(SEQ ID NO:2950)
I037B04	1310	144-251	167-177	193-199	232-240	1-128	26-35	50-66	99-117 DPGYDILTGYPHYGMDV	(SEQ ID NO:2922)
I037C04	1311	142-252	164-177	193-199	232-241	1-126	26-35	50-65	98-115 ENGDDYDILTGQTFYGMVDV	(SEQ ID NO:2752)
I037C06	1312	141-249	163-173	189-195	228-238	1-125	26-35	50-66	99-114 LTYDILTGYYHDAFDI	(SEQ ID NO:2882)
I037C08	1313	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113 DGIDILLVPAALMDV	(SEQ ID NO:2160)
I037D11	1314	136-246	158-171	187-193	226-235	1-120	26-35	50-66	99-109 SQWLEHDVFDI	(SEQ ID NO:2864)
I037E06	1315	144-251	165-175	191-197	230-240	1-128	26-35	50-66	99-117 DRRDYDLTRYYYGMDV	(SEQ ID NO:2928)
I037F04	1316	144-251	165-175	191-197	230-240	1-128	26-35	50-65	98-117 KQRGDYDILTGVLGYAFDI	(SEQ ID NO:2808)
I037G01	1317	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 SHYDILTRLNYYWFDL	(SEQ ID NO:2950)
I037G03	1318	146-256	168-181	197-203	236-245	1-130	26-35	50-66	99-119 DLGSFYDILTALRLNYYGMDV	(SEQ ID NO:2963)
I037G10	1319	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113 DYYDILTKLPYGMVDV	(SEQ ID NO:2975)
I042A07	1320	144-251	167-177	193-199	232-240	1-128	26-35	50-66	99-117 VSPSYDILTGYYLPHAFDV	(SEQ ID NO:2849)
I042A10	1321	142-249	165-175	191-197	230-238	1-126	26-35	50-65	98-115 GPRYDILTGYYNWFDP	(SEQ ID NO:2801)
I042B03	1322	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113 DIDDILTGYYVLGMDV	(SEQ ID NO:2924)
I042B12	1323	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 SHYDILTGLNYYWFDL	(SEQ ID NO:2166)
I042D01	1324	136-246	158-171	187-193	226-235	1-120	26-35	50-66	99-109 QQWLPYDAFDI	(SEQ ID NO:2839)
I042D03	1325	140-250	162-175	191-197	230-239	1-124	26-35	50-68	101-113 ATYDILTGYYFFDI	(SEQ ID NO:2873)
I042D10	1326	142-252	164-177	193-199	232-241	1-126	26-35	50-65	98-115 ERADYDILTGYYFYGMVDV	(SEQ ID NO:2802)
I042E10	1327	147-257	169-182	198-204	237-246	1-131	26-37	52-69	102-120 ERPPYDILTGYYTVTYGMVDV	(SEQ ID NO:2798)
I042E11	1328	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113 DEYDILTGLLQGMVDV	(SEQ ID NO:2883)
I042F08	1329	142-252	164-177	193-199	232-241	1-126	26-37	52-67	100-115 GDYDILTGYYPLHAFDI	(SEQ ID NO:2738)
I042F12	1330	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113 DGYDILTGYYFGMDV	(SEQ ID NO:2976)
I042G08	1331	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 EHYDILTGYSLLGMDV	(SEQ ID NO:2907)
I042G10	1332	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 SHYDILTGLNYYWFDL	(SEQ ID NO:2166)
I042H03	1333	143-253	165-178	194-200	233-242	1-127	26-35	50-65	98-116 GSLYYDILTGYYIGNAFDI	(SEQ ID NO:2759)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I043A03	1334	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	DGYDILTGPFYIYGMVDV (SEQ ID NO:2899)
I043B02	1335	142-249	163-173	189-195	228-238	1-126	26-35	50-65	98-115	GGYDILTGVLVYIYGMVDV (SEQ ID NO:2744)
I043B03	1336	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I043B06	1337	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116	DQYDILTGYYHIDYIYMDV (SEQ ID NO:2828)
I043B07	1338	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I043B09	1339	143-253	165-178	194-200	233-242	1-127	26-35	50-65	98-116	HVRDYDILTGYYRHHFDY (SEQ ID NO:2727)
I043D11	1340	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	EVRYDILTRSYLAGPLDN (SEQ ID NO:2751)
I043E05	1341	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116	TESNYDILTGYYWPSMDV (SEQ ID NO:2940)
I043F01	1342	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I043F04	1343	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I043F12	1344	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116	TESNYDILTGYYWPSMDV (SEQ ID NO:2940)
I043H07	1345	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I044A11	1346	144-251	165-175	191-197	230-240	1-128	26-35	50-68	101-117	APYDILTGYSFYGMVDV (SEQ ID NO:2968)
I044B11	1347	139-249	161-173	189-195	228-238	1-123	26-35	50-66	99-112	DSARLAALDAFDI (SEQ ID NO:2978)
I044C09	1348	140-250	162-174	190-196	229-239	1-124	26-35	50-66	99-113	GQFGLPNYYHYMDV (SEQ ID NO:2943)
I044C10	1349	143-253	165-177	193-199	232-242	1-127	26-35	50-66	99-116	DIKRYNSNWPYDYIYMDV (SEQ ID NO:2726)
I044D03	1350	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	DKQYDILTGDPVEGGMDV (SEQ ID NO:2889)
I044D09	1351	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I044E07	1352	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	AGSSLVTYGTDV (SEQ ID NO:2825)
I044E11	1353	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116	SDYDILTGYYVGLLDY (SEQ ID NO:2758)
I044F07	1354	147-257	169-182	198-204	237-246	1-131	26-35	50-66	99-120	DGRLSYDILTGYYARDYIYGMVDV (SEQ ID NO:2912)
I044G02	1355	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I044G07	1356	149-259	171-184	200-206	239-248	1-133	26-35	50-66	99-122	DQNHPIYDILTGYYVTPGLELKN (SEQ ID NO:2845)
I044H01	1357	144-251	165-175	191-197	230-240	1-128	26-35	50-66	99-117	EVRYDILTRSYLAGPLDN (SEQ ID NO:2751)
I050A01	1358	142-253	164-177	193-199	232-242	1-125	26-35	50-66	99-114	DMGYDILTGYYGAFDI (SEQ ID NO:2946)
I050B12	1359	142-253	164-177	193-199	232-242	1-125	26-35	50-66	99-114	DYYDVLTFGLDGMVDV (SEQ ID NO:2829)
I050C06	1360	142-248	165-175	191-197	230-237	1-124	26-35	50-65	98-113	DHYDVLTFGLQAFDV (SEQ ID NO:2728)
I050C08	1361	142-253	164-177	193-199	232-242	1-125	26-37	52-67	100-114	GRYDPLTGYYLRNFDY (SEQ ID NO:2731)
I050E01	1362	141-252	163-176	192-198	231-241	1-124	26-35	50-66	99-113	GHYDILTGYYFGFDY (SEQ ID NO:2886)
I050E10	1363	138-248	160-172	188-194	227-237	1-121	26-35	50-66	99-110	DMKYVYKVALDV (SEQ ID NO:2823)
I050H08	1364	142-253	164-177	193-199	232-242	1-125	26-35	50-66	99-114	DLRYDILTGYYHDAFDI (SEQ ID NO:2890)
I051A04	1365	148-258	170-183	199-205	238-247	1-131	26-35	50-66	99-120	SSPPKWDALTGHSYHSAMDV (SEQ ID NO:2159)
I051A08	1366	142-252	164-176	192-198	231-241	1-125	26-35	50-66	99-114	HRRARVVVPVPGAMDV (SEQ ID NO:2930)
I051A12	1367	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116	DGSYDILTGYYIDNYMDV (SEQ ID NO:2154)
I051B08	1368	143-253	165-177	193-199	232-242	1-126	26-36	51-67	100-115	RSMIVVTTAPYDAFDL (SEQ ID NO:2785)
I051C06	1369	136-246	158-170	186-192	225-235	1-119	26-35	50-66	99-108	DTVRSGGMDV (SEQ ID NO:2804)
I051G12	1370	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116	DGSYDILTGYYIDNYMDV (SEQ ID NO:2154)
I055A05	1371	134-244	156-169	185-191	224-233	1-117	26-35	50-66	99-106	SGPGWFDP (SEQ ID NO:2870)
I055A11	1372	134-244	156-169	185-191	224-233	1-117	26-35	50-66	99-106	SGPGWFDP (SEQ ID NO:2870)
I061A03	1373	141-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGSSIVGATTGALDM (SEQ ID NO:2852)
I061A04	1374	143-251	165-175	191-197	230-240	1-125	26-35	50-66	99-114	GDYDILTGYPACFQI (SEQ ID NO:2854)
I061A08	1375	142-253	164-176	192-198	233-242	1-124	26-35	50-66	99-113	DNYDILTGYSRRFPD (SEQ ID NO:2942)
I061A09	1376	142-252	164-176	192-198	231-241	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I061A10	1377	141-249	163-173	189-195	228-238	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I061B07	1378	141-252	163-176	192-198	231-241	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I061B09	1379	143-253	165-178	194-200	233-242	1-127	24-33	48-64	97-116	EGGNYDILTGYYIGNAPDI (SEQ ID NO:2158)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I061B12	1380	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I061C12	1381	138-248	160-173	189-195	228-237	1-122	26-35	50-66	99-111 TTYDILTYGHFDY	(SEQ ID NO:2788)
I061D01	1382	137-247	159-172	188-194	227-236	1-121	26-35	50-68	101-110 GPGVIGNYDY	(SEQ ID NO:2749)
I061D03	1383	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I061D04	1384	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113 AVLRYISAGLQGAFDI	(SEQ ID NO:2970)
I061D07	1385	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114 VSGYNSGYFESYDMDV	(SEQ ID NO:2732)
I061D09	1386	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 LNLEKTVVRGFGYFDL	(SEQ ID NO:2952)
I061D10	1387	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 DHYDILTYGLYYGMDV	(SEQ ID NO:2760)
I061E01	1388	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 LNLEKTVVRGFGYFDL	(SEQ ID NO:2952)
I061E05	1389	142-251	163-175	191-197	230-240	1-126	26-35	50-66	99-115 GGELVWFESDYDGMDV	(SEQ ID NO:2787)
I061E09	1390	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I061E12	1391	133-240	154-164	180-186	219-229	1-117	26-35	50-66	99-106 SQLRFIDS	(SEQ ID NO:2842)
I061F01	1392	146-256	168-181	197-203	236-245	1-130	26-35	50-66	99-119 DRYDILTYGYYIPGLDDAFDI	(SEQ ID NO:2887)
I061F09	1393	139-246	160-170	186-192	225-235	1-123	26-35	50-66	99-112 DSDARLAALDAFDI	(SEQ ID NO:2978)
I061F10	1394	145-252	166-176	192-198	231-241	1-129	26-35	50-66	99-118 EESYDILTYGYYVHYGMDV	(SEQ ID NO:2743)
I061F11	1395	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYYFDGFDI	(SEQ ID NO:2949)
I061G01	1396	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I061G03	1397	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 AYYDILTYGLPYDMDL	(SEQ ID NO:2771)
I061G09	1398	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117 EVRNYDLLTRSYLAGPLDN	(SEQ ID NO:2751)
I061G10	1399	143-253	165-178	194-200	233-242	1-127	26-35	50-65	98-116 EGSYDILTYGYYGVGRMDV	(SEQ ID NO:2171)
I061G11	1400	137-247	159-171	187-193	226-236	1-121	26-35	50-68	101-110 RDILTYGYDS	(SEQ ID NO:2933)
I061H05	1401	142-252	164-177	193-199	232-241	1-126	26-37	52-67	100-115 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I064A05	1402	142-249	163-173	189-195	228-238	1-126	26-35	50-68	101-115 DFYDILTYGQHGMVDV	(SEQ ID NO:2919)
I064A11	1403	138-248	160-173	189-195	228-237	1-122	26-35	50-66	99-111 HSKYENWNYALDY	(SEQ ID NO:2754)
I064B01	1404	138-248	160-173	189-195	228-237	1-122	26-35	50-66	99-111 TRMDVLTRYYSDF	(SEQ ID NO:2750)
I064B02	1405	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117 AFEDYDILTYGYHHDFAFDI	(SEQ ID NO:2911)
I064B12	1406	133-243	155-168	184-190	223-232	1-117	26-35	50-66	99-106 PSYHYMDV	(SEQ ID NO:2740)
I064C06	1407	145-255	167-180	196-202	235-244	1-129	26-35	50-66	99-118 VNADYDILTYGPRDYGMVDV	(SEQ ID NO:2819)
I064D01	1408	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I064D02	1409	146-256	168-181	197-203	236-245	1-130	26-35	50-66	99-119 EDATYYDILTYGMYGMDV	(SEQ ID NO:2763)
I064E01	1410	143-250	166-176	192-198	231-239	1-127	26-35	50-66	99-116 ETRKYTSSPPYNYGMDV	(SEQ ID NO:2736)
I064E02	1411	140-251	162-174	190-196	229-240	1-124	26-35	50-66	99-113 RDYDILTYGSRGFDI	(SEQ ID NO:2725)
I064E03	1412	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117 DGIYDILTYLWVSYNGMDV	(SEQ ID NO:2775)
I064E07	1413	140-250	162-175	191-197	230-239	1-124	26-35	50-65	98-113 GERDILTYGLDGMVDV	(SEQ ID NO:2948)
I064E08	1414	140-250	162-174	190-196	229-239	1-124	26-35	50-66	99-113 ERGSYSSGYSGAFDV	(SEQ ID NO:2898)
I064F05	1415	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115 ESGGYSYSGRDYGMVDV	(SEQ ID NO:2836)
I064F08	1416	145-252	166-176	192-198	231-241	1-129	26-35	50-66	99-118 DRGVGYDILTYGTYGMDV	(SEQ ID NO:2900)
I064G06	1417	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I065A12	1418	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116 DVSGHDILTYGYSRYFDV	(SEQ ID NO:2795)
I065C04	1419	139-249	161-173	189-195	228-238	1-123	26-35	50-66	99-112 GQKYYESSGYLH	(SEQ ID NO:2916)
I065C09	1420	140-250	162-174	190-196	229-239	1-124	26-35	50-66	99-113 GDYDILTYGYSHPDY	(SEQ ID NO:2908)
I065E02	1421	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114 AYDYDILTYGYSYFDY	(SEQ ID NO:2895)
I065E04	1422	135-245	157-169	185-191	224-234	1-119	26-35	50-66	99-108 GMDHYGMDV	(SEQ ID NO:2161)
I065F03	1423	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110 AGSSLMYGTGV	(SEQ ID NO:2773)
I065G06	1424	135-242	156-166	182-188	221-231	1-119	26-35	50-66	99-108 GMDHYGMDV	(SEQ ID NO:2161)
I065G07	1425	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115 GGNVDILTYGYYGAFDI	(SEQ ID NO:2824)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I065G08	1426	139-246	160-170	186-192	225-235	1-123	26-35	50-66	99-112 SRDLLLPHYGMDV	(SEQ ID NO:2133)
I065H06	1427	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117 GYEYDILTGYNELGAFDI	(SEQ ID NO:2851)
I066A03	1428	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117 DGYDYDILTGYNQYGMVDV	(SEQ ID NO:2915)
I066A08	1429	137-247	159-171	187-193	226-236	1-121	26-35	50-66	99-110 AGSSLMITYGTDV	(SEQ ID NO:2773)
I066A09	1430	135-245	157-169	185-191	224-234	1-119	26-35	50-66	99-108 GMGDHYGMDV	(SEQ ID NO:2161)
I066A10	1431	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115 DRGYDILTGYYYGMDV	(SEQ ID NO:2876)
I066A11	1432	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116 EVRDYDILTGYYSYMDV	(SEQ ID NO:2778)
I066B02	1433	135-242	156-166	182-188	221-231	1-119	26-35	50-66	99-108 GMGDHYGMDV	(SEQ ID NO:2161)
I066B08	1434	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110 AGSSLMITYGTDV	(SEQ ID NO:2773)
I066B10	1435	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115 GLYFEDTNYRHGDAFDI	(SEQ ID NO:2790)
I066C02	1436	135-245	157-169	185-191	224-234	1-119	26-35	50-66	99-108 GMGDHYGMDV	(SEQ ID NO:2161)
I066C11	1437	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I066C12	1438	135-242	156-166	182-188	221-231	1-119	26-35	50-66	99-108 GMGDHYGMDV	(SEQ ID NO:2161)
I066D06	1439	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113 ENYDFLTGYGAFDI	(SEQ ID NO:2772)
I066D08	1440	138-248	160-173	189-195	228-237	1-122	26-35	50-66	99-111 HSKEYWNWYALDY	(SEQ ID NO:2754)
I066D11	1441	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117 ERSQDFLTGVDRYHPMDV	(SEQ ID NO:2956)
I066D12	1442	139-249	161-174	190-196	229-238	1-123	26-35	50-66	99-112 EGAADYLNQYFQH	(SEQ ID NO:2815)
I066E06	1443	137-247	159-171	187-193	226-236	1-121	26-35	50-66	99-110 AGSSLMITYGTDV	(SEQ ID NO:2773)
I066E12	1444	135-242	156-166	182-188	221-231	1-119	26-35	50-66	99-108 GMGDHYGMDV	(SEQ ID NO:2161)
I066G05	1445	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115 GLYFEDTNYRHGDAFDI	(SEQ ID NO:2790)
I066G08	1446	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114 VYDILTGHPTYGMDV	(SEQ ID NO:2791)
I066G10	1447	144-254	166-178	194-200	233-243	1-128	26-35	50-68	101-117 GIYDILTGHWDADFID	(SEQ ID NO:2872)
I066G12	1448	143-254	165-177	193-199	232-243	1-127	26-35	50-66	99-116 ESTYDILTGSHYDGLDV	(SEQ ID NO:2822)
I066H04	1449	143-253	165-178	194-200	233-242	1-127	26-35	50-65	98-116 DRLHYDILTGHQTDADFID	(SEQ ID NO:2885)
I067A07	1450	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117 VLTNYDILTGYREDADFDM	(SEQ ID NO:2939)
I067A11	1451	135-245	157-170	186-192	225-234	1-119	26-35	50-66	99-108 GMGDHYGMDV	(SEQ ID NO:2161)
I067B08	1452	149-259	171-184	200-206	239-248	1-133	26-35	50-66	99-122 DRGASNYDILTGYPAQGVAFDI	(SEQ ID NO:2969)
I067C08	1453	148-258	170-183	199-205	238-247	1-132	26-37	52-69	102-121 EGAHYDILTGHNYYHYGMDV	(SEQ ID NO:2747)
I067C09	1454	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116 ETRKYTSSPPYNYMYMDV	(SEQ ID NO:2736)
I067D07	1455	137-247	159-171	187-193	226-236	1-121	26-35	50-66	99-110 AGSSLMITYGTDV	(SEQ ID NO:2773)
I067E01	1456	142-248	164-174	190-196	229-238	1-124	26-35	50-66	99-113 DQHDILTGVYYGMDV	(SEQ ID NO:2921)
I067E06	1457	135-245	157-169	185-191	224-234	1-119	26-35	50-66	99-108 GMGDHYGMDV	(SEQ ID NO:2161)
I067E07	1458	150-260	172-184	200-206	239-249	1-134	26-35	50-67	100-123 DYPGSEYDILTGVLFGYYGMDV	(SEQ ID NO:2926)
I067E11	1459	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I067G03	1460	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113 ARRVGLVGGKNAFEI	(SEQ ID NO:2765)
I067G05	1461	140-250	162-174	190-196	229-239	1-124	26-35	50-66	99-113 DQHDILTGVYYGMDV	(SEQ ID NO:2894)
I067G12	1462	141-252	163-176	192-198	231-241	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I067H05	1463	146-256	168-180	196-202	235-245	1-130	26-35	50-68	101-119 EGTYYDILTGYPLGYFDY	(SEQ ID NO:2936)
I067H06	1464	135-245	157-169	185-191	224-234	1-119	26-35	50-66	99-108 GMGDHYGMDV	(SEQ ID NO:2161)
I068C09	1465	138-248	160-172	188-194	227-237	1-121	26-35	50-66	99-110 GGSSQNIFYGMDV	(SEQ ID NO:2884)
I068G03	1466	144-254	166-178	194-200	233-243	1-127	26-35	50-66	99-116 GTGYDILTGYMGSAFDQ	(SEQ ID NO:2800)
I068G04	1467	143-252	165-178	194-200	233-241	1-126	26-35	50-66	99-115 GVWVAYGDVGIYGFVDV	(SEQ ID NO:2937)
I068G07	1468	142-251	164-174	190-196	229-240	1-124	26-35	50-66	99-113 HDYYIMTAARHYIDS	(SEQ ID NO:2909)
I068G08	1469	144-254	166-178	194-200	233-243	1-127	26-35	50-66	99-116 GIGYDLLTGYFTGSPLDY	(SEQ ID NO:2846)
I070F07	1470	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113 DFYDILTGYHDAFDI	(SEQ ID NO:2910)
I070G05	1471	140-250	162-175	191-197	230-239	1-124	26-35	50-68	101-113 DVDDILTGYSHDY	(SEQ ID NO:2867)

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TABLE 1-continued

scFvs that Immunospecifically Bind to 8 Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I070H02	1472	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 MEYDILTGYGGYFPDY	(SEQ ID NO:2179)
I071A01	1473	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 AAYDPLTGYSPDGFPI	(SEQ ID NO:2783)
I071A03	1474	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116 DMHYDILTGYTGLAFDM	(SEQ ID NO:2917)
I071B08	1475	144-252	166-176	192-198	231-241	1-126	27-36	51-67	100-115 GGYDILTQYPAEFFHP	(SEQ ID NO:2764)
I071E01	1476	138-248	160-173	189-195	228-237	1-122	26-35	50-66	99-111 DFGVIGDYRPFDPY	(SEQ ID NO:2777)
I071F11	1477	135-245	157-169	185-191	224-234	1-119	26-35	50-66	99-108 SSNPVYGLDV	(SEQ ID NO:2957)
I071G11	1478	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSPDGFPI	(SEQ ID NO:2153)
I071H08	1479	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSPDGFPI	(SEQ ID NO:2153)
I074A02	1480	142-250	164-174	190-196	229-239	1-125	26-35	50-66	99-114 DORDILTNYLYEFQH	(SEQ ID NO:2868)
I074A08	1481	148-259	170-182	198-204	237-248	1-131	26-35	50-66	99-120 SSPPKWDALTDGSSYHSAMDV	(SEQ ID NO:2165)
I074D10	1482	146-253	168-178	194-200	233-242	1-128	26-35	50-66	99-117 DKTIGDQLVEAYYDGMV	(SEQ ID NO:2776)
I074E01	1483	146-255	168-178	194-200	233-244	1-128	26-35	50-66	99-117 LGRISRDLLTGYHFNMDV	(SEQ ID NO:2944)
I074E02	1484	142-250	164-174	190-196	229-239	1-124	26-35	50-66	99-113 DDYDILTGLSYFPDS	(SEQ ID NO:2803)
I074E08	1485	144-259	166-179	195-205	240-248	1-127	26-35	50-66	99-116 GTGYDILTGYMGSAPDQ	(SEQ ID NO:2800)
I074F12	1486	142-250	164-174	190-196	229-239	1-124	26-35	50-66	99-113 DRADILTYNDAPDI	(SEQ ID NO:2739)
I074H06	1487	140-251	162-175	191-197	230-240	1-123	26-35	50-66	99-112 RYGDPFYTYMNV	(SEQ ID NO:2755)
I074H07	1488	145-253	167-177	193-199	232-242	1-127	26-35	50-66	99-116 GTGYDILTGYMGSAPDQ	(SEQ ID NO:2800)
I074H08	1489	143-254	165-178	194-200	233-243	1-126	26-35	50-66	99-115 VSNIDILTWGGYNWFDQ	(SEQ ID NO:2955)
I075A07	1490	145-253	167-177	193-199	232-242	1-127	26-35	50-66	99-116 GTGYDILTGYMGSAPDQ	(SEQ ID NO:2800)
I075B01	1491	134-244	156-168	184-190	223-233	1-117	26-35	50-66	99-106 DQGRYLDL	(SEQ ID NO:2175)
I075B04	1492	134-247	156-169	185-191	224-236	1-117	26-35	50-66	99-106 DQGRYLDL	(SEQ ID NO:2175)
I075B06	1493	141-252	163-175	191-197	230-241	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I075B08	1494	144-257	166-179	195-201	234-246	1-127	26-35	50-66	99-116 GTGYDILTGYMGSAPDQ	(SEQ ID NO:2800)
I075B09	1495	142-252	164-176	192-198	231-241	1-125	26-35	50-66	99-114 TYDILTGYAEPQH	(SEQ ID NO:2932)
I075B12	1496	141-251	163-176	192-198	231-240	1-124	26-35	50-66	99-113 SDYDILTGYWPAV	(SEQ ID NO:2812)
I075C01	1497	148-259	170-183	199-205	238-248	1-131	26-35	50-66	99-120 GREDTKVKPWRDYFHYTYNDV	(SEQ ID NO:2835)
I075C05	1498	134-244	156-168	184-190	223-233	1-117	26-35	50-66	99-106 DQGRYLDL	(SEQ ID NO:2175)
I075D05	1499	145-253	168-179	195-201	234-242	1-127	26-35	50-66	99-116 GTGYDILTGYMGSVDP	(SEQ ID NO:2897)
I075D07	1500	142-252	164-176	192-198	231-241	1-125	26-35	50-66	99-114 SYDILTGYHTPLDY	(SEQ ID NO:2853)
I075D08	1501	141-251	163-175	191-197	230-240	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I075E01	1502	145-253	167-177	193-199	232-242	1-127	26-35	50-66	99-116 GTGYDILTGYMGSAPDQ	(SEQ ID NO:2800)
I075E03	1503	150-261	172-184	200-206	239-250	1-132	28-37	52-68	101-121 GGGYDILTGYSPYLYYGLDV	(SEQ ID NO:2865)
I075E04	1504	144-255	166-179	195-201	234-244	1-127	26-35	50-66	99-116 GRGYDVLTYFTGSPLDY	(SEQ ID NO:2881)
I075E05	1505	141-252	163-176	192-198	231-241	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I075E10	1506	141-252	163-176	192-198	231-241	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I075E11	1507	134-244	156-168	184-190	223-233	1-117	26-35	50-66	99-106 SGPGWFDQ	(SEQ ID NO:2870)
I075E12	1508	143-254	165-178	194-200	233-243	1-126	26-35	50-66	99-115 TDRFGAKDVTARWGMV	(SEQ ID NO:2979)
I075F02	1509	146-253	168-178	194-200	233-242	1-128	26-35	50-66	99-117 EQGYDILTGYYPEGGWFDQ	(SEQ ID NO:2834)
I075F04	1510	142-251	164-176	192-198	231-240	1-125	26-37	52-67	100-114 AGYDLLTGYPPYFDS	(SEQ ID NO:2757)
I075F06	1511	146-254	168-178	194-200	233-243	1-128	26-35	50-66	99-117 GRNYDFTGYNPNLGLDY	(SEQ ID NO:2830)
I075F07	1512	141-251	163-175	191-197	230-240	1-124	26-35	50-66	99-113 ENYDSLTYGNYFDY	(SEQ ID NO:2971)
I075F08	1513	134-244	156-168	184-190	223-233	1-117	26-35	50-66	99-106 DQKKAQDI	(SEQ ID NO:2779)
I075F09	1514	147-257	169-181	197-203	236-246	1-129	26-35	50-66	99-118 LKAPYYDILLTYHLPKWFDQ	(SEQ ID NO:2953)
I075F10	1515	135-243	157-167	183-189	222-232	1-117	26-35	50-66	99-106 DQGRYLDL	(SEQ ID NO:2175)
I075F11	1516	134-245	156-169	185-191	224-234	1-117	26-35	50-66	99-106 DQGRYLDL	(SEQ ID NO:2175)
I075G05	1517	141-252	163-175	191-197	230-241	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I075G07	1518	141-252	163-175	191-197	230-241	1-124	26-35	50-66	99-113 GRYYDMLTRGGYFDY	(SEQ ID NO:2858)
I075G08	1519	141-252	163-176	192-198	231-241	1-124	26-35	50-66	99-113 RQYDILTGYYGGFDY	(SEQ ID NO:2958)
I075G11	1520	142-253	164-177	193-199	232-242	1-125	26-35	50-66	99-114 TDYDILTGYPNGYFDP	(SEQ ID NO:2173)
I075G12	1521	134-245	156-169	185-191	224-234	1-117	26-35	50-66	99-106 DQGRYLDL	(SEQ ID NO:2175)
I075H02	1522	144-254	166-178	194-200	233-243	1-127	26-35	50-66	99-116 GTGYDILTGYYMGSAFDQ	(SEQ ID NO:2800)
I075H03	1523	134-245	156-169	185-191	224-234	1-117	26-35	50-66	99-106 DQGRYLDL	(SEQ ID NO:2175)
I075H06	1524	134-244	156-168	184-190	223-233	1-117	26-35	50-66	99-106 DQGRYLDL	(SEQ ID NO:2175)
I075H08	1525	144-254	166-179	195-201	234-243	1-127	26-35	50-66	99-116 GSGYDLLTGYPFGSPLDY	(SEQ ID NO:2766)
I076A01	1526	144-253	166-176	192-198	231-242	1-126	26-35	50-66	99-115 DRRRDDLTGYLYDAFDS	(SEQ ID NO:2878)
I076A03	1527	137-247	159-171	187-193	226-236	1-119	26-35	50-68	101-108 GYDTAMQY	(SEQ ID NO:2951)
I076A06	1528	134-245	156-168	184-190	223-234	1-117	26-35	50-66	99-106 DQGRYLDL	(SEQ ID NO:2175)
I076A07	1529	140-250	162-174	190-196	229-239	1-123	26-35	50-66	99-112 DRRDILTGSNFGQD	(SEQ ID NO:2913)
I076A08	1530	144-253	166-176	192-198	231-242	1-126	26-35	50-66	99-115 MGHVDILTGYPHYGMDV	(SEQ ID NO:2831)
I076B01	1531	145-257	167-179	195-201	236-246	1-127	26-35	50-66	99-116 GSGYDLLTGYPFGSPLDY	(SEQ ID NO:2766)
I076B03	1532	134-245	156-169	185-191	224-234	1-117	26-35	50-66	99-106 DQGRYLDL	(SEQ ID NO:2175)
I076B07	1533	135-243	157-167	183-189	222-232	1-117	26-35	50-66	99-106 DQGRYLDL	(SEQ ID NO:2175)
I076B08	1534	143-252	166-177	193-199	232-241	1-125	26-35	50-66	99-114 PYYDPLTAYTFQYFGN	(SEQ ID NO:2806)
I076C04	1535	142-250	164-174	190-196	229-239	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I076C10	1536	141-251	163-175	191-197	230-240	1-124	26-35	50-66	99-113 GRYYDMLTRGGYFDY	(SEQ ID NO:2858)
I076D01	1537	142-252	164-176	192-198	231-241	1-125	26-35	50-66	99-114 LDYDILTGYPFGFDY	(SEQ ID NO:2799)
I076D08	1538	141-251	163-175	191-197	230-240	1-124	26-37	52-67	100-113 RFYDLLTGYSAPDS	(SEQ ID NO:2756)
I076D11	1539	144-255	166-179	195-201	234-244	1-127	26-35	50-66	99-116 GTGYDILTGYYMGSAFDQ	(SEQ ID NO:2800)
I076D12	1540	142-250	164-174	190-196	229-239	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I076E04	1541	145-252	167-177	193-199	232-241	1-127	26-35	50-66	99-116 GTGYDILTGYYMGSAFDQ	(SEQ ID NO:2800)
I076E07	1542	141-251	163-175	191-197	230-240	1-124	26-35	50-66	99-113 EYDVLTLGLFYMDV	(SEQ ID NO:2841)
I076E09	1543	142-253	164-177	193-199	232-242	1-125	26-35	50-66	99-114 DRRDILTNLYEYFQH	(SEQ ID NO:2868)
I076E11	1544	144-254	166-179	195-201	234-243	1-127	26-35	50-66	99-116 GTGYDILTGYYMGSAFDQ	(SEQ ID NO:2800)
I076F01	1545	144-253	166-178	194-199	232-242	1-127	26-35	50-66	99-116 GTGYDILTGYYMGSAFDQ	(SEQ ID NO:2800)
I076F03	1546	141-251	163-175	191-197	230-240	1-124	26-36	51-66	99-113 GDYDVLTLGYLRKLDY	(SEQ ID NO:2742)
I076F04	1547	135-245	157-169	185-191	224-234	1-117	26-35	50-66	99-106 DQGRYLDL	(SEQ ID NO:2175)
I076F08	1548	142-250	164-174	190-196	229-239	1-124	26-36	51-66	99-113 VHYDILTYLWAFDI	(SEQ ID NO:2730)
I076F10	1549	141-252	163-175	191-197	230-241	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I076G09	1550	134-245	156-168	184-190	223-234	1-117	26-35	50-66	99-106 DQGRYLDL	(SEQ ID NO:2175)
I076G10	1551	141-251	163-175	191-197	230-240	1-124	26-35	50-66	99-113 GRYYDMLTRGGYFDY	(SEQ ID NO:2858)
I076G11	1552	144-259	166-179	195-205	240-248	1-127	26-35	50-66	99-116 GTGYDILTGYYMGSAFDQ	(SEQ ID NO:2800)
I076G12	1553	147-257	169-181	197-203	236-246	1-130	26-35	50-66	99-119 NGYDILTGYYLWDYGYGMDV	(SEQ ID NO:2769)
I076H02	1554	141-251	163-175	191-197	230-240	1-124	26-35	50-66	99-113 ENYDILTGYYNYFDY	(SEQ ID NO:2971)
I076H04	1555	143-251	165-175	191-197	230-240	1-125	26-35	50-66	99-114 THYDILTGYYSHPLDY	(SEQ ID NO:2863)
I076H05	1556	141-251	163-175	191-197	230-240	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I076H06	1557	141-252	163-176	192-198	231-241	1-124	26-35	50-66	99-113 VPDYDILTYNGAFDV	(SEQ ID NO:2827)
I076H09	1558	144-256	166-179	195-201	234-245	1-127	26-35	50-66	99-116 GSGYDLLTGYPFGSPLDY	(SEQ ID NO:2766)
I076H10	1559	144-256	166-179	195-201	234-245	1-127	26-35	50-66	99-116 GSGYDLLTGYPFGSPLDY	(SEQ ID NO:2766)
I077D06	1560	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113 VYYDILTGYNLFFDY	(SEQ ID NO:2177)
I078B04	1561	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113 VYYDILTGYNLFFDY	(SEQ ID NO:2177)
I078E10	1562	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 MEYDILTGYYGGYFDY	(SEQ ID NO:2179)
I002A01-K	1563	142-250	164-174	190-196	229-239	1-125	26-35	50-66	99-114 ELGLSIVGATTGALDM	(SEQ ID NO:2174)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I002A01-R	1564	142-250	164-174	190-196	229-239	1-125	26-35	50-66	99-114	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I026C04-K	1565	142-250	164-176	192-198	231-239	1-125	26-35	50-66	99-114	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I026C04-R	1566	142-250	164-176	192-198	231-239	1-125	26-35	50-66	99-114	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I067B10	1567	149-259	171-183	199-205	238-248	1-133	26-35	50-66	99-122	DRGAPNYDILTGYYPAGQVAFDI (SEQ ID NO:2176)
I068C06	1568	134-244	156-169	185-191	224-233	1-117	26-35	50-66	99-106	DQGRYLDL (SEQ ID NO:2175)
I075F12	1569	134-244	156-168	184-190	223-233	1-117	26-35	50-66	99-106	DQGRYLDL (SEQ ID NO:2175)
I003C06	1570	141-249	163-173	189-195	228-238	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I025B06	1571	141-249	163-175	191-197	230-238	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I025B09	1572	141-249	163-175	191-197	230-238	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I026C04	1573	141-249	163-175	191-197	230-238	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I027B12	1574	142-250	164-174	190-196	229-239	1-125	26-34	49-65	99-114	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I030A10	1575	141-252	163-176	192-198	231-241	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I064C04	1576	147-257	169-182	198-204	237-246	1-131	26-35	50-66	99-120	DGRLSYDILTGYIARYYGMDD (SEQ ID NO:2188)
I064C07	1577	134-241	157-167	183-189	222-230	1-118	26-35	50-66	99-107	SEGTIRGVD (SEQ ID NO:2178)
I065D04	1578	144-254	166-179	195-201	234-243	1-128	26-36	51-66	99-117	KGYYDILTGYRDNWFD (SEQ ID NO:2181)
I065D08	1579	147-257	169-182	198-204	237-246	1-131	26-35	50-66	99-120	TPSSVYDILTGYHYFYSYMDV (SEQ ID NO:2189)
I065F08	1580	135-242	158-168	184-190	223-231	1-119	26-35	50-66	99-108	EKSAGYFDY (SEQ ID NO:2190)
I067F05	1581	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	ENYDSLTGYGAFDI (SEQ ID NO:2185)
I068B04	1582	134-244	156-168	184-190	223-233	1-117	26-35	50-66	99-106	DQGRYLDL (SEQ ID NO:2175)
I068B08	1583	141-252	163-175	191-197	231-241	1-124	26-34	49-65	98-113	KLGLSIVGATTGALDM (SEQ ID NO:2186)
I068C08	1584	143-254	165-178	194-200	233-243	1-126	26-35	50-66	99-115	EGMNDPINSHHYTMDA (SEQ ID NO:2182)
I068F03	1585	140-251	162-175	191-197	230-240	1-123	26-35	50-66	99-112	AGNEYGHTERPADY (SEQ ID NO:2180)
I069B07	1586	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	MEYDILTGYGGYFDY (SEQ ID NO:2179)
I071B03	1587	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSPDGFDI (SEQ ID NO:2153)
I072B09	1588	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSPDGFDI (SEQ ID NO:2153)
I073F04	1589	136-246	158-171	187-193	226-235	1-120	26-35	50-66	99-109	SLATRLGMDV (SEQ ID NO:2184)
I074B12	1590	142-252	164-176	192-198	231-241	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I075A02	1591	141-251	163-175	191-197	230-240	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I075G01	1592	142-251	164-174	190-196	229-240	1-124	26-35	50-66	99-113	DHFDILTGYFRRLDS (SEQ ID NO:2187)
I078D02	1593	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	VYDILTGYNLFFDY (SEQ ID NO:2177)
I078D08	1594	144-251	165-175	191-197	230-240	1-128	26-35	50-66	99-117	DAQSYDILTGYQSYAFDI (SEQ ID NO:2183)
I078H08	1595	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	VYDILTGYNLFFDY (SEQ ID NO:2177)
I064A03	1596	150-257	171-181	197-203	236-246	1-134	26-35	50-66	99-123	GPSTTYDILTGYTPYYYYYMDV (SEQ ID NO:3014)
I064B03	1597	145-255	167-179	195-201	234-244	1-129	26-37	52-67	100-118	HVRDYDILTGYRGHYFDY (SEQ ID NO:2167)
I064B05	1598	140-250	162-174	190-196	229-239	1-124	26-35	50-66	99-113	ERGVWTAYGDSFDL (SEQ ID NO:2985)
I064B11	1599	138-248	160-173	189-195	228-237	1-122	26-35	50-66	99-111	DRGPGLSSPFES (SEQ ID NO:3033)
I064C02	1600	146-256	168-180	196-202	235-245	1-130	26-35	50-66	99-119	DEYDILTGYQAPYYYYGMDV (SEQ ID NO:3068)
I064C03	1601	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	ERGVWTAYGDSFDL (SEQ ID NO:2985)
I064C11	1602	143-253	165-178	194-200	233-242	1-127	26-35	50-65	98-116	DVTYHDILTGYAGHEAFDI (SEQ ID NO:3055)
I064C12	1603	148-255	171-181	197-203	236-244	1-132	26-37	52-69	102-121	ESGRYDILTGYSGGGGMDV (SEQ ID NO:3012)
I064D03	1604	146-256	168-181	197-203	236-245	1-130	26-35	50-66	99-119	DGANYDILTGYTTTVGMDV (SEQ ID NO:3072)
I064D04	1605	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	RSYDILTGYTYGMDV (SEQ ID NO:3090)
I064D06	1606	134-244	156-169	185-191	224-233	1-118	26-35	50-66	99-107	EGSSGYLVG (SEQ ID NO:2981)
I064E05	1607	146-256	168-180	196-202	235-245	1-130	26-37	52-67	100-119	KQRGDYDILTGYQLGYAFDI (SEQ ID NO:2808)
I064E06	1608	145-255	167-180	196-202	235-244	1-129	26-35	50-66	99-118	ERPGYDILTGYPSIYGMV (SEQ ID NO:3053)
I064F07	1609	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSPDGFDI (SEQ ID NO:2153)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scPv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I064F09	1610	147-257	169-181	197-203	236-246	1-131	26-35	50-66	99-120	DTLGYDILTGYPPPPYYDMDV (SEQ ID NO:2988)
I064F10	1611	143-253	165-177	193-199	232-242	1-127	22-31	46-62	95-116	DTLGYDILTGYPPPPYYDMDV (SEQ ID NO:2988)
I064F11	1612	142-252	164-177	193-199	232-241	1-126	26-35	50-65	98-115	GRHYDILTGYNEAFDI (SEQ ID NO:3031)
I064G01	1613	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	NYVDVLTQSYGMDV (SEQ ID NO:3077)
I064G04	1614	133-243	155-167	183-189	222-232	1-117	26-35	50-66	99-106	DNSGTGY (SEQ ID NO:3084)
I064G08	1615	138-245	159-169	185-191	224-234	1-122	26-35	50-66	99-111	GGTAGRSVYFDS (SEQ ID NO:2990)
I064G10	1616	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	SPNGDYSYGAWGLE (SEQ ID NO:3085)
I064G11	1617	138-248	160-173	189-195	228-237	1-122	26-35	50-65	98-111	YPDGSGYVPVSFSY (SEQ ID NO:3064)
I064G12	1618	139-249	161-173	189-195	228-238	1-123	26-35	50-65	98-112	VNYDILTGLGYFDY (SEQ ID NO:3049)
I064H03	1619	143-253	165-178	194-200	233-242	1-127	26-37	52-67	100-116	SYDILTGRPYTDAFDI (SEQ ID NO:2989)
I064H04	1620	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	PLGITAVRGAKTDAFGI (SEQ ID NO:2929)
I064H06	1621	149-256	170-180	196-202	235-245	1-133	26-35	50-66	99-122	DRGASNYDILTGYAPAGVAFDI (SEQ ID NO:2969)
I065A02	1622	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSGDFDI (SEQ ID NO:2153)
I065A04	1623	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSGDFDI (SEQ ID NO:2153)
I065A06	1624	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSGDFDI (SEQ ID NO:2153)
I065A07	1625	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	DGGYDILTGYQYYGMDV (SEQ ID NO:2987)
I065B01	1626	145-255	167-180	196-202	235-244	1-129	26-35	50-65	98-118	WATYYDTLTGYRLKDHAGFDI (SEQ ID NO:3017)
I065B05	1627	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	SPGDDILTGYKYTFDY (SEQ ID NO:3032)
I065B09	1628	146-253	167-177	193-199	232-242	1-130	26-35	50-66	99-119	DAGESYDILTGYVIEGYMDV (SEQ ID NO:2986)
I065B12	1629	139-249	161-174	190-196	229-238	1-123	26-35	50-66	99-112	EGAADYLNQYFQH (SEQ ID NO:2815)
I065C02	1630	136-246	158-170	186-192	225-235	1-120	26-35	50-66	99-109	EGSNSGLDLDY (SEQ ID NO:3007)
I065C06	1631	141-253	163-175	191-197	230-242	1-125	26-35	50-66	99-114	ATYDPLTGYSGDFDI (SEQ ID NO:2153)
I065C08	1632	141-250	163-176	192-198	231-239	1-125	26-35	50-66	99-114	VSGYNSGYFESYDMDV (SEQ ID NO:2732)
I065C10	1633	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	QGGQYDSPPLDV (SEQ ID NO:3002)
I065D01	1634	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	DRDYDILTGYNYGMDV (SEQ ID NO:3074)
I065D03	1635	142-249	165-175	191-197	230-238	1-126	26-35	50-66	99-115	APLYDILTGYIIGNDY (SEQ ID NO:3028)
I065D05	1636	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116	DKDYDILTGYWDELDDY (SEQ ID NO:3040)
I065D06	1637	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	DPNYDILTGYYYAMDV (SEQ ID NO:3062)
I065E01	1638	139-246	160-170	186-192	225-235	1-123	26-35	50-66	99-112	EPDQLLARGHGMDV (SEQ ID NO:3027)
I065E05	1639	137-244	158-168	184-190	223-233	1-121	26-35	50-66	99-110	AGSLMTYGTDV (SEQ ID NO:2773)
I065E06	1640	146-256	168-181	197-203	236-245	1-130	26-35	50-66	99-119	ARGSYDILTGYRPGDGYFDY (SEQ ID NO:3043)
I065E08	1641	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	GLYFEDTNYRHGDAFDI (SEQ ID NO:2790)
I065E09	1642	145-255	167-179	195-201	234-244	1-129	26-35	50-65	98-118	ERSYDILTGYSPRSKYGMDV (SEQ ID NO:3021)
I065E12	1643	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSGDFDI (SEQ ID NO:2153)
I065F04	1644	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	ERGVTAYGDSFDL (SEQ ID NO:2985)
I065F05	1645	140-250	162-175	191-197	230-239	1-124	26-35	50-65	98-113	RYSDALTYSLGAFDV (SEQ ID NO:3018)
I065F07	1646	145-252	166-176	192-198	231-241	1-129	26-38	53-69	102-118	GAYYDILTGYYPYGMVDV (SEQ ID NO:2860)
I065F09	1647	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116	DYPIDVLTGRRTKWFDP (SEQ ID NO:3013)
I065F12	1648	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	DQVDRLLMQYNYMDA (SEQ ID NO:3047)
I065G01	1649	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSGDFDI (SEQ ID NO:2153)
I065G09	1650	143-253	165-178	194-200	233-242	1-127	26-35	50-68	101-116	DAYYDILTGWVYGMVDV (SEQ ID NO:3030)
I065G10	1651	140-247	161-171	187-193	226-236	1-124	26-36	51-66	99-113	FRYDILTGYMDV (SEQ ID NO:2983)
I065H05	1652	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113	EYYDILTGYSGAFDI (SEQ ID NO:2984)
I065H07	1653	138-248	160-173	189-195	228-237	1-122	26-35	50-66	99-111	TRMDVLTTRYSDP (SEQ ID NO:2750)
I066A05	1654	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	AGSLMTYGTDV (SEQ ID NO:2773)
I066A06	1655	139-246	160-170	186-192	225-235	1-123	26-35	50-66	99-112	EGAADYLNQYFQH (SEQ ID NO:2815)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I066A12	1656	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	DTRVIGIQLWERGAFDM (SEQ ID NO:3080)
I066B05	1657	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I066B11	1658	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	PLGITAVRGAKTDAFGI (SEQ ID NO:2929)
I066C06	1659	144-254	166-178	194-200	233-243	1-128	26-35	50-65	98-117	GRRYYDILTGYSLGRGEMDV (SEQ ID NO:3009)
I066C10	1660	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I066D02	1661	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	AGTSLMNYGTDV (SEQ ID NO:3048)
I066D07	1662	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	GPYDVLTLGYSNGFDY (SEQ ID NO:2992)
I066E01	1663	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	QGGQYDSPPFDV (SEQ ID NO:3001)
I066E03	1664	149-259	171-184	200-206	239-248	1-133	26-35	50-66	99-122	GEKARYDYDILTGYSYSAWGGYYMDV (SEQ ID NO:3045)
I066E04	1665	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	LNLEKTVIRGPGYFDL (SEQ ID NO:3081)
I066E05	1666	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	VGGYDILTGYYLRGMDV (SEQ ID NO:2997)
I066E07	1667	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I066E09	1668	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I066F01	1669	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	SPYDILTGYYVNGVDV (SEQ ID NO:3058)
I066F03	1670	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I066F04	1671	141-251	163-175	191-197	230-240	1-125	26-35	50-66	99-114	VAAAGARTLGYPGMDV (SEQ ID NO:3071)
I066F07	1672	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116	DVSGHDILTGYSYRYFDV (SEQ ID NO:2795)
I066F08	1673	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	SPMYDRLTGFYPSGYFDS (SEQ ID NO:3036)
I066F11	1674	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	GAYYDILTGYYPYGMDV (SEQ ID NO:2860)
I066F12	1675	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	GPSSAGTTIGLGSFDP (SEQ ID NO:3005)
I066G06	1676	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116	ETRYKTSPPYNYNYMDV (SEQ ID NO:2736)
I066G07	1677	133-243	155-168	184-190	223-232	1-117	26-30	45-61	94-106	DQFSVGGRHAFDL (SEQ ID NO:3054)
I066H02	1678	135-242	156-166	182-188	221-231	1-119	26-35	50-66	99-108	GMGDHYGMDV (SEQ ID NO:2161)
I067A02	1679	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I067A03	1680	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	AGSSLMTYGTDV (SEQ ID NO:2773)
I067A06	1681	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I067A08	1682	137-247	159-171	187-193	226-236	1-121	26-35	50-66	99-110	AGSSLMTYGTDV (SEQ ID NO:2773)
I067A10	1683	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113	ERGVTAYGGSFDL (SEQ ID NO:2985)
I067B03	1684	142-253	164-177	193-199	232-242	1-126	26-35	50-66	99-115	PLGITAVRGAKTDAFGI (SEQ ID NO:2929)
I067B04	1685	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	AGSSLMTYGTDV (SEQ ID NO:2773)
I067C03	1686	134-244	156-169	185-191	224-233	1-117	26-35	50-66	99-106	DWGHWFDP (SEQ ID NO:2982)
I067C05	1687	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	SGSSLMTYGTDV (SEQ ID NO:3015)
I067C07	1688	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	EPYDILTGYYGSYFDY (SEQ ID NO:3041)
I067C10	1689	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	AGSSLMTYGTDV (SEQ ID NO:2773)
I067C12	1690	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	TYIDILTGYSGGAFDY (SEQ ID NO:3024)
I067D01	1691	136-246	158-171	187-193	226-235	1-120	26-35	50-66	99-109	GSRVRGVTPDL (SEQ ID NO:3020)
I067D03	1692	137-244	158-168	184-190	223-233	1-121	26-35	50-66	99-110	AGSSLMTYGTDV (SEQ ID NO:2773)
I067D05	1693	146-256	168-180	196-202	235-245	1-130	26-35	50-66	99-119	ECSSGSCPARQPPYYQYYMDV (SEQ ID NO:2993)
I067D06	1694	137-244	158-168	184-190	223-233	1-121	26-35	50-66	99-110	AGSSLMTYGTDV (SEQ ID NO:2773)
I067D09	1695	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	GAYYDILTGYYPYGMDV (SEQ ID NO:2860)
I067D12	1696	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	QGGQYDSPPLDV (SEQ ID NO:3002)
I067E02	1697	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	AGSSLMTYGTDV (SEQ ID NO:2773)
I067E04	1698	142-252	164-176	192-198	231-241	1-126	26-35	50-66	99-115	GAYYDILTGYYPYGMDV (SEQ ID NO:2860)
I067E05	1699	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	DYRNYDILTGHPYYGMDV (SEQ ID NO:2996)
I067F01	1700	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	QHYDILTGYSQEPFDI (SEQ ID NO:3022)
I067F03	1701	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	DQTYDILTGHHYYGMDV (SEQ ID NO:3087)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I067F04	1702	139-246	160-170	186-192	225-235	1-123	26-35	50-66	99-112	EGAADYLNQYFQH (SEQ ID NO:2815)
I067F08	1703	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113	LGYYDILTGYSDDY (SEQ ID NO:3029)
I067F10	1704	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	AGSSLMAYGTDV (SEQ ID NO:3016)
I067F11	1705	140-248	161-171	187-193	226-237	1-124	26-35	50-66	99-113	ENYDFLTGYGAFDI (SEQ ID NO:2772)
I067G01	1706	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)
I067G09	1707	137-247	159-171	187-193	226-236	1-121	26-35	50-66	99-110	AGSSLMTYGTDV (SEQ ID NO:2773)
I067H07	1708	144-251	165-175	191-197	230-240	1-128	26-35	50-66	99-117	GGLYDILTGRPATDDAFDI (SEQ ID NO:3035)
I068A07	1709	143-254	165-178	194-200	233-243	1-126	26-35	50-66	99-115	TDRFGAKDVTARWGMV (SEQ ID NO:2979)
I068E05	1710	148-257	170-183	199-205	238-246	1-131	26-35	50-66	99-120	GREDTKVKPWDRYYHYNDV (SEQ ID NO:2809)
I068E08	1711	135-247	157-169	185-193	226-236	1-117	26-35	50-66	99-106	DQGRYLDL (SEQ ID NO:2175)
I068E11	1712	141-251	163-176	192-198	231-240	1-124	26-34	49-65	98-113	ELGLSTVGATTGALDM (SEQ ID NO:2174)
I068F04	1713	142-252	164-176	192-198	231-241	1-125	26-35	50-66	99-114	ELGHREGGYWSPYNV (SEQ ID NO:2838)
I068G05	1714	137-245	159-169	185-191	224-234	1-119	26-35	50-66	98-108	KMGSASAAADF (SEQ ID NO:3042)
I068G06	1715	140-250	162-174	190-196	229-239	1-123	26-35	50-66	99-112	RYGDPPFYHYMMNV (SEQ ID NO:2755)
I068G11	1716	147-258	169-182	198-204	237-247	1-130	26-35	50-66	99-119	ESGSHYDLLTGLLVAANGFDV (SEQ ID NO:3044)
I069A09	1717	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDY (SEQ ID NO:2179)
I069A10	1718	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDY (SEQ ID NO:2179)
I069B06	1719	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDY (SEQ ID NO:2179)
I069B09	1720	139-249	161-174	190-196	229-238	1-123	26-35	50-66	99-112	PYYDILTGYPAFDI (SEQ ID NO:3026)
I069B12	1721	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDY (SEQ ID NO:2179)
I069C06	1722	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116	VLPHYDILTGYSQNWFDV (SEQ ID NO:3000)
I069C09	1723	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116	VLPHYDILTGYSQNWFDV (SEQ ID NO:3000)
I069D03	1724	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	DGYDILTGYSYGMV (SEQ ID NO:2135)
I069E09	1725	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	DGYDILTGYSYGMV (SEQ ID NO:2135)
I069E11	1726	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113	VYYDILTGYNLFDDY (SEQ ID NO:2177)
I069F05	1727	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDY (SEQ ID NO:2179)
I069F07	1728	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDY (SEQ ID NO:2179)
I069F12	1729	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113	GYDILTGYYDAFDI (SEQ ID NO:3051)
I069G06	1730	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115	DGYDILTGYSYGMV (SEQ ID NO:3059)
I069G08	1731	145-252	166-176	192-198	231-241	1-129	26-35	50-66	99-118	DRLEYDILTGYYHYGMV (SEQ ID NO:3039)
I069G11	1732	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDY (SEQ ID NO:2179)
I070A03	1733	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDY (SEQ ID NO:2179)
I070A09	1734	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDY (SEQ ID NO:2179)
I070B01	1735	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	SQSDYDILTGYYHYGMV (SEQ ID NO:3038)
I070B05	1736	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDY (SEQ ID NO:2179)
I070D03	1737	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDY (SEQ ID NO:2179)
I070D04	1738	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	MEYDILTSYGGYFDY (SEQ ID NO:3034)
I070E01	1739	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117	SQSDYDILTGYYHYGMV (SEQ ID NO:3038)
I070F01	1740	144-251	165-175	191-197	230-240	1-128	26-35	50-66	99-117	SQSNYDILTGYYHYGMV (SEQ ID NO:3067)
I070G10	1741	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	MEYDILTGYYGGYFDY (SEQ ID NO:2179)
I071A06	1742	135-242	156-166	182-188	221-231	1-119	26-35	50-66	99-108	GMGDHYGMV (SEQ ID NO:2161)
I071B02	1743	135-245	157-170	186-192	225-234	1-119	26-35	50-66	99-108	GMGDHYGMV (SEQ ID NO:2161)
I071D02	1744	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	AGTSLMNYGTDV (SEQ ID NO:3048)
I071D08	1745	146-256	168-181	197-203	236-245	1-130	26-37	52-66	99-119	VPYYDTSGGYLGEYHYGMV (SEQ ID NO:3010)
I071F01	1746	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110	AGTSLMNYGTDV (SEQ ID NO:3048)
I071G09	1747	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	ATYDPLTGYSFDGFDI (SEQ ID NO:2153)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I072A01	1748	139-249	161-174	190-196	229-238	1-123	26-35	50-66	99-112 SRDLLLPHYGMDV	(SEQ ID NO:2133)
I072A09	1749	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I072B02	1750	135-245	157-170	186-192	225-234	1-119	26-35	50-66	99-108 GMGDHYGMDV	(SEQ ID NO:2161)
I072B10	1751	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110 AGSSLMYTGTDV	(SEQ ID NO:2773)
I072B11	1752	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I072B12	1753	140-249	162-173	189-195	228-238	1-124	26-35	50-66	99-113 ENYDYLTYGYGAFDI	(SEQ ID NO:2995)
I072C05	1754	135-245	157-169	185-191	224-234	1-119	26-35	50-66	99-108 GMGDHYGMDV	(SEQ ID NO:2161)
I072C10	1755	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I072D01	1756	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I072D05	1757	135-245	157-169	185-191	224-234	1-119	26-35	50-66	99-108 GMGDHYGMDV	(SEQ ID NO:2161)
I072E01	1758	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I072E04	1759	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117 EGSYDILTYGYVGVGRMDV	(SEQ ID NO:2171)
I072E05	1760	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I072E06	1761	135-242	156-166	182-188	221-231	1-119	26-35	50-66	99-108 GMGDHYGMDV	(SEQ ID NO:2161)
I072F03	1762	135-242	156-166	182-188	221-231	1-119	26-35	50-66	99-108 GMGDHYGMDV	(SEQ ID NO:2161)
I072F07	1763	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I072F11	1764	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113 DEYDILTGLLQGMV	(SEQ ID NO:2883)
I072G03	1765	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I072G04	1766	137-247	159-171	187-193	226-236	1-121	26-35	50-68	101-110 RDILTYGYDS	(SEQ ID NO:2933)
I072G05	1767	137-247	159-171	187-193	226-236	1-121	26-35	50-66	99-110 GYRNDWYGAFDI	(SEQ ID NO:3079)
I072G09	1768	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I072H03	1769	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I072H07	1770	137-247	159-172	188-194	227-236	1-121	26-35	50-66	99-110 AGTSLMNYGMDV	(SEQ ID NO:3070)
I073A02	1771	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114 GPYDILTYGYRDAFDI	(SEQ ID NO:2998)
I073A03	1772	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115 THYDILTYGYTADAFDI	(SEQ ID NO:3019)
I073A04	1773	148-258	170-183	199-205	238-247	1-132	26-35	50-66	99-121 VQMDSEYDILLTGINVGPPYFDY	(SEQ ID NO:2132)
I073A05	1774	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I073A06	1775	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I073A09	1776	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I073A10	1777	146-253	167-177	193-199	232-242	1-130	26-35	50-66	99-119 GDFGDYDILTYGYPPVYIGMDV	(SEQ ID NO:3082)
I073A11	1778	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114 SYDILTYGYPPGMDV	(SEQ ID NO:3004)
I073B02	1779	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117 DLWYYDILTYGYLLDDAFDI	(SEQ ID NO:2999)
I073B05	1780	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117 DLWYYDILTYGYLLDDAFDI	(SEQ ID NO:2999)
I073B06	1781	139-246	160-170	186-192	225-235	1-123	26-35	50-66	99-112 SRDLLLPHYGMDV	(SEQ ID NO:2133)
I073B07	1782	138-248	160-173	189-195	228-237	1-122	26-35	50-66	99-111 TRMDVLTRYYSDF	(SEQ ID NO:2750)
I073B08	1783	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I073B11	1784	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I073C01	1785	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 GYHDTLTSYNNWFDP	(SEQ ID NO:3006)
I073C02	1786	148-255	169-179	195-201	234-244	1-132	26-35	50-66	99-121 AQMDSEYDILLTGINVGPPYFDY	(SEQ ID NO:3076)
I073C04	1787	142-252	164-177	193-199	232-241	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I073C07	1788	134-241	155-165	181-187	220-230	1-118	26-35	50-66	99-107 GMGDHYMDV	(SEQ ID NO:3008)
I073C08	1789	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115 EMGYDILTYGYLNYMDV	(SEQ ID NO:2862)
I073C09	1790	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 QHYDILTYGYSQEPFDI	(SEQ ID NO:3022)
I073C11	1791	146-256	168-181	197-203	236-245	1-130	26-35	50-68	101-119 FNPTYDILTYGYIGGYFQH	(SEQ ID NO:2155)
I073C12	1792	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I073D01	1793	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I073D03	1794	135-245	157-169	185-191	224-234	1-119	26-35	50-66	99-108 GMGDHYGMDV	(SEQ ID NO:2161)
I073D06	1795	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I073D08	1796	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117 EVRNYDLLTRSYLAGPLDN	(SEQ ID NO:2751)
I073D10	1797	140-250	162-175	191-197	230-239	1-124	26-35	50-68	101-113 QYDILTGVELDI	(SEQ ID NO:3073)
I073D11	1798	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I073E01	1799	148-258	170-183	199-205	238-247	1-132	26-37	52-69	102-121 EGAHYDILTGHNYYHYGMDV	(SEQ ID NO:2747)
I073E02	1800	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I073E03	1801	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:3003)
I073E05	1802	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 QHYDILTGYSQEPFDI	(SEQ ID NO:3022)
I073E06	1803	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I073E08	1804	140-250	162-175	191-197	230-239	1-124	26-35	50-66	99-113 ENYDPLTGYYGAFDI	(SEQ ID NO:2772)
I073F01	1805	141-251	163-175	191-197	230-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I073F02	1806	141-251	163-175	191-197	230-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I073F03	1807	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I073F05	1808	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I073F07	1809	141-251	163-175	191-197	230-240	1-125	26-35	50-66	99-114 GEYDILTGYPYWFDL	(SEQ ID NO:3023)
I073F09	1810	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I073F11	1811	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I073F12	1812	141-251	163-175	191-197	230-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I073G03	1813	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116 DGSYDILTGYYIDNHYMDV	(SEQ ID NO:2154)
I073G04	1814	143-253	165-178	194-200	233-242	1-127	26-35	50-65	98-116 GEGGYDILTGRLRGYGMV	(SEQ ID NO:3037)
I073G05	1815	135-245	157-169	185-191	224-234	1-119	26-35	50-66	99-108 GMGDHYGMDV	(SEQ ID NO:2161)
I073G06	1816	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I073G07	1817	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115 GSYDILTGISLGMV	(SEQ ID NO:3063)
I073G08	1818	139-246	160-170	186-192	225-235	1-123	26-35	50-66	99-112 SRDLLLPHYGMV	(SEQ ID NO:2133)
I073G09	1819	145-255	167-180	196-202	235-244	1-129	26-35	50-66	99-118 DRGHYDILTGYYIEPSPGFY	(SEQ ID NO:3061)
I073G10	1820	135-245	157-170	186-192	225-234	1-119	26-35	50-66	99-108 GPGVIGNYDY	(SEQ ID NO:2749)
I073G12	1821	142-252	164-177	193-199	232-241	1-126	26-35	50-68	101-115 GGMIRAREDDYYMDV	(SEQ ID NO:3083)
I073H01	1822	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I073H03	1823	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I073H05	1824	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I073H06	1825	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I073H07	1826	138-245	159-169	185-191	224-234	1-122	26-35	50-66	99-111 TYDILTGYYFDY	(SEQ ID NO:3056)
I073H08	1827	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114 ATYDPLTGYSFDGFDI	(SEQ ID NO:2153)
I074A05	1828	144-255	166-179	195-201	234-244	1-127	26-35	50-66	99-116 LPPYDMLTGYYVGGGMDV	(SEQ ID NO:3050)
I074A06	1829	145-253	167-177	193-199	232-242	1-127	26-35	50-66	99-116 AKPYTDFSRGSDADAFDV	(SEQ ID NO:3065)
I074B03	1830	134-242	156-166	182-188	221-231	1-117	26-35	50-66	99-106 DQGRYLDL	(SEQ ID NO:2175)
I074B11	1831	140-251	162-175	191-197	230-240	1-123	26-35	50-66	99-112 RYGDPPFYYYMYNV	(SEQ ID NO:2755)
I074C07	1832	141-251	163-175	191-197	230-240	1-124	26-34	49-65	98-113 ELGLSIVGATTGALDM	(SEQ ID NO:2174)
I074D03	1833	143-251	165-175	191-197	230-240	1-125	26-35	50-66	99-114 GGYDILTGYPAEFFHP	(SEQ ID NO:2764)
I074D04	1834	134-246	156-169	185-191	224-235	1-117	26-35	50-66	99-106 DQGRYLDL	(SEQ ID NO:2175)
I074D05	1835	145-253	167-177	193-199	232-242	1-127	26-35	50-66	99-116 DRYDILTKGDDYYGMDV	(SEQ ID NO:3060)
I074D07	1836	151-262	173-186	202-208	241-251	1-134	26-35	50-66	99-123 VQGETYYDILTGYYGPKRDLYGMDV	(SEQ ID NO:3069)
I074D08	1837	141-251	163-175	191-197	230-240	1-124	26-34	49-65	98-113 ELGLSIVVATTGALDM	(SEQ ID NO:2980)
I074D11	1838	139-249	161-174	190-196	229-238	1-122	26-35	50-66	99-111 ESEGGDYTNPFY	(SEQ ID NO:2991)
I074E05	1839	134-245	156-169	185-191	224-234	1-117	26-35	50-66	99-106 DQGRYLDL	(SEQ ID NO:2175)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I074E07	1840	141-251	163-175	191-197	230-240	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I074E09	1841	147-258	169-182	198-204	237-247	1-130	26-35	50-68	101-119	DPGNYDILTGYYTYGMDV (SEQ ID NO:2935)
I074E11	1842	138-244	160-170	186-192	225-233	1-121	26-35	50-66	99-110	VRLPHHHYFMAV (SEQ ID NO:3075)
I074H05	1843	144-254	166-178	194-200	233-243	1-126	26-35	50-66	99-115	ESSITVNPYYFYGMDV (SEQ ID NO:3025)
I075A03	1844	135-242	158-168	184-190	223-231	1-117	26-35	50-66	99-106	DQGRYLDL (SEQ ID NO:2175)
I075A10	1845	135-244	157-169	185-191	224-233	1-117	26-35	50-66	99-106	DQGRYLDL (SEQ ID NO:2175)
I075B07	1846	144-254	166-178	194-200	233-243	1-127	26-35	50-66	99-116	SPEGDYQPLSSNYNWLD (SEQ ID NO:3011)
I075D11	1847	134-246	156-169	185-191	224-235	1-117	26-36	51-66	99-106	GKEGYNDN (SEQ ID NO:3089)
I075D12	1848	145-253	167-177	193-199	232-242	1-127	26-35	50-66	99-116	GSQYDILLTGYYFTGSPLDY (SEQ ID NO:2766)
I075G02	1849	144-255	166-179	195-201	234-244	1-127	26-35	50-66	99-116	SPEGDYQPLSSNYNWLD (SEQ ID NO:3011)
I075G09	1850	143-253	165-177	193-199	232-242	1-126	26-35	50-66	99-115	MCHVDILTGYRHYGMDV (SEQ ID NO:2831)
I075G10	1851	140-250	162-174	190-196	229-239	1-122	26-35	50-66	99-111	GHYDILTGYPHDL (SEQ ID NO:3086)
I075H05	1852	142-252	164-176	192-198	231-241	1-125	26-35	50-66	99-114	SYDILTGYHTPLDY (SEQ ID NO:2853)
I075H07	1853	145-253	167-177	193-199	232-242	1-127	26-35	50-66	99-116	GSQYDILLTGYYFTGSPLDY (SEQ ID NO:2766)
I076A11	1854	142-254	164-177	193-199	232-243	1-125	26-35	50-66	99-114	DDRDLITNYLYEYFQH (SEQ ID NO:2868)
I076A12	1855	144-256	166-178	194-200	233-245	1-127	26-35	50-66	99-116	GSQYDVLTYFTGSPLDY (SEQ ID NO:3057)
I076B06	1856	142-249	164-174	190-196	229-238	1-124	26-35	50-66	99-113	GRYDILTGYFTSFDY (SEQ ID NO:3066)
I076B10	1857	142-254	164-177	193-199	232-243	1-125	26-35	50-66	99-114	DDRDLITNYLYEYFQH (SEQ ID NO:2868)
I076B12	1858	145-253	167-177	193-199	232-242	1-127	26-35	50-66	99-116	GTGYDILTGYMGSAFDQ (SEQ ID NO:2800)
I076C06	1859	143-253	165-177	193-199	232-242	1-126	26-35	50-66	99-115	MCHVDILTGYRHYGMDV (SEQ ID NO:2831)
I076C11	1860	134-245	156-168	184-190	223-234	1-117	26-35	50-66	99-106	DQGRYLDL (SEQ ID NO:2175)
I076D06	1861	141-252	163-176	192-198	231-241	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I076E05	1862	144-255	166-179	195-201	234-244	1-127	26-35	50-66	99-116	GTGYDILTGYMGSAFDQ (SEQ ID NO:2800)
I076E08	1863	135-243	157-167	183-189	222-232	1-117	26-35	50-66	99-106	DQGRYLDL (SEQ ID NO:2175)
I076F06	1864	134-245	156-169	185-191	224-234	1-117	26-36	51-66	99-106	RDVQGAPE (SEQ ID NO:3088)
I076G01	1865	144-254	166-178	194-200	233-243	1-127	26-35	50-66	99-116	VEGYDILTGYSFDAFDI (SEQ ID NO:3078)
I076H01	1866	146-254	168-178	194-200	233-243	1-128	26-35	50-66	99-117	EQGYDILTGYYPGGWFD (SEQ ID NO:2834)
I076H03	1867	142-250	164-174	190-196	229-239	1-124	26-34	49-65	98-113	ELGLSIVGATTGALDM (SEQ ID NO:2174)
I077B05	1868	147-257	169-182	198-204	237-246	1-131	26-37	52-69	102-120	DKSYDILTGYTYTYGMDV (SEQ ID NO:3052)
I077C10	1869	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	MEYDILTGYGGYFDY (SEQ ID NO:2179)
I077D01	1870	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	MEYDILTGYGGYFDY (SEQ ID NO:2179)
I077D04	1871	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	MEYDILTGYGGYFDY (SEQ ID NO:2179)
I077D11	1872	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	MEYDILTGYGGYFDY (SEQ ID NO:2179)
I077D12	1873	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113	EKYDILTGYDAFDI (SEQ ID NO:3046)
I077E01	1874	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	EMGYDILTGYLLNYMDV (SEQ ID NO:2862)
I077E03	1875	142-252	164-177	193-199	232-241	1-126	26-35	50-66	99-115	EMGYDILTGYLLNYMDV (SEQ ID NO:2862)
I077E08	1876	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	MEYDILTGYGGYFDY (SEQ ID NO:2179)
I077F05	1877	141-248	162-172	188-194	227-237	1-125	26-35	50-66	99-114	MEYDILTGYGGYFDY (SEQ ID NO:2179)
I077G06	1878	141-251	163-176	192-198	231-240	1-125	26-35	50-66	99-114	MEYDILTGYGGYFDY (SEQ ID NO:2179)
I077H02	1879	141-248	164-174	190-196	229-237	1-125	26-35	50-66	99-114	MEYDILTGYGGYFDY (SEQ ID NO:2179)
I078B05	1880	143-253	165-178	194-200	233-242	1-127	26-35	50-66	99-116	ESHYDILTGYYSNPSPDI (SEQ ID NO:2994)
I079E02	1881	137-244	160-170	186-192	225-233	1-121	26-35	50-66	99-116	DSGSYYDAFDI (SEQ ID NO:2194)
I079F11	1882	132-239	155-165	181-187	220-228	1-116	26-35	50-66	99-105	TGSGFDY (SEQ ID NO:2192)
I082G02	1883	136-243	159-169	185-191	224-232	1-120	26-35	50-66	99-109	DGYRTNDALDI (SEQ ID NO:2191)
I082H08	1884	132-242	154-167	183-189	222-231	1-115	26-35	50-66	99-104	DWDMDV (SEQ ID NO:2193)
I099D03	1885	137-247	159-172	188-194	227-236	1-120	26-35	50-66	99-109	DNGGGTIGFDY (SEQ ID NO:2195)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I079B05	1886	130-240	152-165	181-187	220-229	1-114	26-35	50-66	99-103 FVL DY	(SEQ ID NO:2210)
I079B12	1887	134-241	157-167	183-189	222-230	1-118	26-35	50-66	99-107 WTSSGAFDI	(SEQ ID NO:2205)
I079C01	1888	131-241	153-166	182-188	221-230	1-115	26-35	50-66	99-104 DWDMDV	(SEQ ID NO:2193)
I079F06	1889	134-241	157-167	183-189	222-230	1-118	26-35	50-66	99-107 DNLHAAFDI	(SEQ ID NO:2202)
I079F08	1890	138-248	160-172	188-194	227-237	1-122	26-35	50-66	99-111 YYHSSGSDAFDI	(SEQ ID NO:2206)
I080A03	1891	139-249	161-173	189-195	228-238	1-122	26-35	50-66	99-111 VGIAAAVDNFEY	(SEQ ID NO:2197)
I080A08	1892	136-247	158-171	187-193	226-236	1-119	26-35	50-66	99-108 VHSYGYAFEN	(SEQ ID NO:2200)
I080B01	1893	144-254	166-178	194-200	233-243	1-126	26-35	50-66	99-115 EYSGYHYVEGGSYAMDV	(SEQ ID NO:2201)
I080D03	1894	139-249	161-173	189-195	228-238	1-122	26-35	50-66	99-111 VGIAAAVDNFEY	(SEQ ID NO:2197)
I080E05	1895	142-253	164-177	193-199	232-242	1-125	26-35	50-66	99-114 EGGGDAYDVAPYYFDY	(SEQ ID NO:2204)
I080G07	1896	138-245	161-172	188-194	227-234	1-120	26-35	50-66	99-109 EGPGYYGYMDV	(SEQ ID NO:2209)
I080G09	1897	137-249	159-172	188-194	227-238	1-120	26-35	50-66	99-109 DNGGGTIGFDY	(SEQ ID NO:2195)
I082A05	1898	131-240	153-165	181-187	220-229	1-115	26-35	50-66	99-104 DLDYDY	(SEQ ID NO:2208)
I082B08	1899	137-247	159-171	187-193	226-236	1-121	26-35	50-66	99-110 DLGIAGTIYFDY	(SEQ ID NO:2207)
I082C03	1900	138-245	161-171	187-193	226-234	1-122	26-35	50-66	99-111 DASRDIVVLPLAI	(SEQ ID NO:2198)
I082D07	1901	134-241	157-167	183-189	222-230	1-118	26-35	50-66	99-107 WTSSGAFDI	(SEQ ID NO:2205)
I082G01	1902	138-245	161-171	187-193	226-234	1-122	26-35	50-66	99-111 DRSGWPNWYFDL	(SEQ ID NO:2212)
I083B12	1903	139-247	161-171	187-193	226-236	1-121	26-35	50-66	99-110 ESGAGGYYYDDY	(SEQ ID NO:2196)
I083G03	1904	139-249	161-173	189-195	228-238	1-122	26-35	50-66	99-111 VGIAAAVDNFEY	(SEQ ID NO:2197)
I084A01	1905	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I084B02	1906	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I084C04	1907	131-238	152-162	178-184	217-227	1-115	25-34	49-65	98-104 NLWGLDY	(SEQ ID NO:2199)
I084C11	1908	134-244	156-169	185-191	224-233	1-118	26-35	50-66	99-107 GNAGAFDI	(SEQ ID NO:2211)
I079A01	1909	134-243	156-168	184-190	223-232	1-118	26-35	50-66	99-107 EGVAAGEDY	(SEQ ID NO:3123)
I079A03	1910	134-244	156-169	185-191	224-233	1-118	26-35	50-66	99-107 GMDWDFDY	(SEQ ID NO:3183)
I079A04	1911	134-241	155-165	181-187	220-230	1-118	26-35	50-66	99-107 VDSSGYATY	(SEQ ID NO:3213)
I079A06	1912	133-240	154-164	180-186	219-229	1-117	26-35	50-66	99-106 DAAVTAEG	(SEQ ID NO:3142)
I079A07	1913	136-246	158-170	186-192	225-235	1-120	26-35	50-66	99-109 GSNYSPDAFDI	(SEQ ID NO:3112)
I079A10	1914	148-255	169-179	195-201	234-244	1-132	26-35	50-68	101-121 LPPDLRYCDGGICPGFDWLGP	(SEQ ID NO:3163)
I079A11	1915	135-242	158-168	184-190	223-231	1-119	26-35	50-66	99-108 GPSYYYMAV	(SEQ ID NO:3114)
I079B02	1916	134-243	156-168	184-190	223-232	1-118	26-35	50-66	99-107 EGVAAGEDY	(SEQ ID NO:3123)
I079B03	1917	136-246	158-170	186-192	225-235	1-120	26-35	50-66	99-109 GSNYSPDAFDI	(SEQ ID NO:3112)
I079B04	1918	130-240	152-165	181-187	220-229	1-114	26-35	50-66	99-103 LLSDY	(SEQ ID NO:3168)
I079B07	1919	138-245	159-169	185-191	224-234	1-122	26-35	50-66	99-111 DLSSGYFSRYFDY	(SEQ ID NO:3193)
I079B09	1920	139-246	162-172	188-194	227-235	1-123	26-35	50-66	99-112 VEVEDIVVGSAPDI	(SEQ ID NO:3128)
I079C02	1921	144-251	167-177	193-199	232-240	1-128	26-35	50-66	99-117 VTSLYSSSSGGYYYGYMDV	(SEQ ID NO:3145)
I079C04	1922	132-239	155-165	181-187	220-228	1-116	26-35	50-66	99-105 GWRGVDY	(SEQ ID NO:3195)
I079C05	1923	140-247	163-173	189-195	228-236	1-124	26-35	50-66	99-113 AGGNPRSGSLVYFDY	(SEQ ID NO:3225)
I079C07	1924	137-244	158-168	184-190	223-233	1-121	26-35	50-66	99-110 GLDVYAIYGLDV	(SEQ ID NO:3176)
I079D01	1925	144-254	166-179	195-201	234-243	1-128	26-35	50-66	99-117 EVRNYDLLTRSYLAGPLDN	(SEQ ID NO:2751)
I079D02	1926	135-245	157-169	185-191	224-234	1-119	26-35	50-66	99-108 EIGWEGAFDI	(SEQ ID NO:3178)
I079D04	1927	133-243	155-167	183-189	222-232	1-117	26-35	50-66	99-106 VRPGLMDV	(SEQ ID NO:3132)
I079D06	1928	137-247	159-171	187-193	226-236	1-121	26-35	50-66	99-110 EAYTSSWAEPDF	(SEQ ID NO:3190)
I079D07	1929	136-243	157-167	183-189	222-232	1-120	26-35	50-66	99-109 NITPLAMVGDF	(SEQ ID NO:3146)
I079D08	1930	130-240	152-165	181-187	220-229	1-114	26-35	50-66	99-103 LIEDF	(SEQ ID NO:3161)
I079D09	1931	131-238	152-162	178-184	217-227	1-115	26-35	50-66	99-104 DSGSPD	(SEQ ID NO:3108)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I079D11	1932	134-241	157-167	183-189	222-230	1-118	26-35	50-66	99-107 EGVAAGEDY	(SEQ ID NO:3123)
I079E06	1933	136-244	158-168	184-190	223-233	1-120	26-35	50-66	99-109 EKRGSRVFDI	(SEQ ID NO:3093)
I079E08	1934	137-247	159-171	187-193	226-236	1-121	26-35	50-66	99-110 EAYASSWAEDF	(SEQ ID NO:3189)
I079E11	1935	136-243	159-169	185-191	224-232	1-120	26-35	50-66	99-109 PYGSGSYAFDI	(SEQ ID NO:3185)
I079E12	1936	143-253	165-177	193-199	232-242	1-127	26-35	50-66	99-116 ARDYDSSGYVVPDAFDI	(SEQ ID NO:3107)
I079F01	1937	133-241	154-164	180-186	219-230	1-117	26-35	50-66	99-106 GHFYGMDV	(SEQ ID NO:3098)
I079F02	1938	148-253	169-179	195-201	234-242	1-132	26-35	50-68	101-121 LPPDLRYCDGSMCSGFDWLGP	(SEQ ID NO:3219)
I079F03	1939	140-247	161-171	187-193	226-236	1-124	26-35	50-66	99-113 ESLLTEEYCGSDCYS	(SEQ ID NO:3115)
I079F04	1940	136-243	157-167	183-189	222-232	1-120	26-35	50-66	99-109 NSAPPAPSMVDV	(SEQ ID NO:3099)
I079F09	1941	130-237	151-161	177-183	216-226	1-114	26-35	50-66	99-103 RYYDY	(SEQ ID NO:3139)
I079F10	1942	136-243	157-167	183-189	222-232	1-120	26-35	50-66	99-109 NITPLAMVGDF	(SEQ ID NO:3146)
I079F12	1943	136-243	159-169	185-191	224-232	1-120	26-35	50-66	99-109 ADYSNDYYMDV	(SEQ ID NO:3166)
I079G02	1944	136-243	157-167	183-189	222-232	1-120	26-35	50-66	99-109 NITPLAMVGDF	(SEQ ID NO:3146)
I079G05	1945	136-243	159-169	185-191	224-232	1-120	26-35	50-66	99-109 FPLESYYMDV	(SEQ ID NO:3124)
I079G06	1946	135-245	157-170	186-192	225-234	1-119	26-35	50-66	99-108 GNSFGRTL DY	(SEQ ID NO:3158)
I079H05	1947	136-243	157-167	183-189	222-232	1-120	26-35	50-66	99-109 DVPPDGYLEV	(SEQ ID NO:3192)
I079H06	1948	134-241	157-167	183-189	222-230	1-118	26-35	50-66	99-107 ASYPVPFDY	(SEQ ID NO:3171)
I080A01	1949	132-242	154-166	182-188	221-231	1-115	26-35	50-66	99-104 GGWLDD	(SEQ ID NO:3210)
I080A02	1950	134-245	156-169	185-191	224-234	1-117	26-35	50-66	99-106 EHSSSF DY	(SEQ ID NO:3111)
I080A05	1951	142-253	164-177	193-199	232-242	1-125	26-35	50-66	99-114 EGEEDGYNVAPYYFDY	(SEQ ID NO:3160)
I080A06	1952	143-250	166-176	192-198	233-239	1-125	26-35	50-66	99-114 EAGSGSYHFSPPFDY	(SEQ ID NO:3188)
I080A07	1953	136-247	158-171	187-193	226-236	1-119	26-35	50-66	99-108 TGIWGYFDY	(SEQ ID NO:3175)
I080A10	1954	142-252	164-176	192-198	231-241	1-125	26-35	50-66	99-114 DGNLNYDGS TDYGMVDV	(SEQ ID NO:3140)
I080B02	1955	140-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111 LGRNYTSSWSLDY	(SEQ ID NO:3181)
I080B03	1956	139-249	161-173	189-195	228-238	1-122	26-35	50-66	99-111 VVGYSSTLGT DV	(SEQ ID NO:3096)
I080B05	1957	139-249	161-173	189-195	228-238	1-121	26-35	50-66	99-110 LGVARGREAFDL	(SEQ ID NO:3206)
I080B06	1958	143-254	165-177	193-199	232-243	1-126	26-37	52-69	102-115 AVRSPGYYYMDV	(SEQ ID NO:3125)
I080B07	1959	135-243	157-167	183-189	222-232	1-117	26-35	50-66	99-106 GRKPLFDY	(SEQ ID NO:3141)
I080B08	1960	137-248	159-172	188-194	227-237	1-120	26-37	52-67	100-109 KQRREKYFDY	(SEQ ID NO:3100)
I080B09	1961	143-254	165-178	194-200	233-243	1-126	26-35	50-66	99-115 EKAIETTSGEADPFDI	(SEQ ID NO:3151)
I080B10	1962	139-249	161-173	189-195	228-238	1-122	26-37	52-67	100-111 RPALRSLWYFDL	(SEQ ID NO:3102)
I080B11	1963	138-248	160-172	188-194	227-237	1-121	26-35	50-68	101-110 LHCTGGSCGF	(SEQ ID NO:3186)
I080B12	1964	141-253	164-179	195-201	234-242	1-123	26-35	50-66	99-112 NPYYDSSEGFFDY	(SEQ ID NO:3109)
I080C03	1965	140-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111 SGRQAYYYGMDV	(SEQ ID NO:3091)
I080C06	1966	146-254	168-178	194-200	233-243	1-128	26-36	51-66	99-117 DYYDGSSYSSG DYYYMDV	(SEQ ID NO:3227)
I080C07	1967	145-256	167-180	196-202	235-245	1-128	26-35	50-66	99-117 DSDLVVIPTAIQGRYYFDN	(SEQ ID NO:3113)
I080C08	1968	138-249	160-173	189-195	228-238	1-121	26-35	50-66	99-110 GKRYSYGWYFDI	(SEQ ID NO:3130)
I080C10	1969	132-243	154-167	183-189	222-232	1-115	26-35	50-66	99-104 DTPLDP	(SEQ ID NO:3094)
I080C11	1970	138-249	160-173	189-195	228-238	1-121	26-35	50-66	99-110 EGDPTDNDAFDV	(SEQ ID NO:3155)
I080C12	1971	139-249	161-173	189-195	228-238	1-122	26-35	50-66	99-111 DGPTYARPPYLDH	(SEQ ID NO:3153)
I080D01	1972	138-245	161-171	187-193	226-234	1-120	26-35	50-66	99-109 DGTKYDWGFDY	(SEQ ID NO:3220)
I080D02	1973	142-254	164-177	193-199	232-243	1-125	26-35	50-66	99-114 ETFSHCSGGSCYFPDY	(SEQ ID NO:3212)
I080D04	1974	140-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111 SGRQAYYYGMDV	(SEQ ID NO:3091)
I080D05	1975	138-246	160-170	186-192	225-235	1-120	26-35	50-66	99-109 EPPGYVYLT DY	(SEQ ID NO:3165)
I080D08	1976	138-248	160-172	188-194	227-237	1-121	26-35	50-68	101-110 LHCTGGSCGF	(SEQ ID NO:3186)
I080D09	1977	139-250	161-174	190-196	229-239	1-122	26-35	50-66	99-111 VDYYDYMGAFFI	(SEQ ID NO:3187)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scPv SEQ ID NO	AA# of VL	AA# of VL CDR1	AA# of VL CDR2	AA# of VL CDR3	AA# of VH	AA# of VH CDR1	AA# of VH CDR2	AA# of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I080D11	1978	136-247	158-171	187-193	226-236	1-119	26-35	50-66	99-108 VGNFGYYFYEY	(SEQ ID NO:3196)
I080D12	1979	137-245	159-169	185-191	224-234	1-119	26-35	50-68	101-108 SSRNGGDY	(SEQ ID NO:3214)
I080E01	1980	138-246	160-170	186-192	225-235	1-120	26-35	50-66	99-109 DLSRVAGRFDY	(SEQ ID NO:3164)
I080E04	1981	137-247	159-171	187-193	226-236	1-120	26-37	52-67	100-109 HDVYGDLPDY	(SEQ ID NO:3211)
I080E06	1982	138-248	160-172	188-194	227-237	1-121	26-35	50-68	101-110 LHCSGGSCGF	(SEQ ID NO:3221)
I080E07	1983	143-254	165-178	194-200	233-243	1-126	26-35	50-66	99-115 EGSIVGATLTINDAFDI	(SEQ ID NO:3150)
I080E08	1984	138-249	160-173	189-195	228-238	1-121	26-35	50-66	99-110 GKRYSYGWYFDI	(SEQ ID NO:3130)
I080E12	1985	132-242	154-166	182-188	221-231	1-114	26-35	50-66	99-103 DPFYD	(SEQ ID NO:3134)
I080F04	1986	139-249	161-173	189-195	228-238	1-122	26-35	50-66	99-111 DGPTYARPYLDH	(SEQ ID NO:3153)
I080F05	1987	143-253	165-177	193-199	232-242	1-126	26-35	50-66	99-115 ESSGTLGEFSLPLPFYD	(SEQ ID NO:3203)
I080F06	1988	140-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111 LGRNYTSSWSLDY	(SEQ ID NO:3181)
I080F08	1989	132-240	154-164	180-186	219-229	1-114	26-35	50-66	99-103 NAFDY	(SEQ ID NO:3121)
I080G03	1990	142-250	164-174	190-196	229-239	1-124	26-36	51-66	99-113 GRGYSSSSSVYGM DI	(SEQ ID NO:3095)
I080G04	1991	133-244	156-171	187-193	226-233	1-115	26-35	50-66	99-104 VHSSGS	(SEQ ID NO:3216)
I080G10	1992	145-252	167-177	193-199	232-241	1-127	26-35	50-66	99-116 KRGDGFGVIRLHHYTGMDV	(SEQ ID NO:3136)
I080G11	1993	137-247	159-171	187-193	226-236	1-120	26-37	52-67	100-109 HDVYGDLPDS	(SEQ ID NO:3205)
I080H01	1994	142-252	164-176	192-198	231-241	1-124	26-37	52-67	100-113 LRPDADYGDYGFYD	(SEQ ID NO:3218)
I080H02	1995	140-248	162-172	188-194	227-237	1-123	26-35	50-66	99-112 TSERGTYRQWDFDN	(SEQ ID NO:3204)
I080H03	1996	136-246	158-170	186-192	225-235	1-119	26-35	50-66	99-108 EAGEVAIDY	(SEQ ID NO:3180)
I080H04	1997	138-249	160-173	189-195	228-238	1-121	26-35	50-66	99-110 GKRYSYGWYFDI	(SEQ ID NO:3130)
I080H05	1998	137-247	159-171	187-193	226-236	1-120	26-37	52-67	100-109 HDVYGDLPDS	(SEQ ID NO:3205)
I080H06	1999	138-249	160-173	189-195	228-238	1-121	26-35	50-66	99-110 GKRYSYGWYFDV	(SEQ ID NO:3217)
I080H07	2000	138-248	160-172	188-194	227-237	1-121	26-35	50-68	101-110 LHCTGGSCGF	(SEQ ID NO:3186)
I080H08	2001	140-251	162-175	191-197	230-240	1-122	26-35	50-66	99-111 ERGGRDGDYALDP	(SEQ ID NO:3148)
I080H09	2002	141-249	163-173	189-195	228-238	1-123	26-36	51-66	99-112 RTPDHNGDSGPPDY	(SEQ ID NO:3215)
I081A01	2003	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I081A03	2004	135-245	157-170	186-192	225-234	1-119	26-35	50-66	99-108 ESLTGGAFDI	(SEQ ID NO:3117)
I081A04	2005	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I081A06	2006	130-237	151-161	177-183	216-226	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I081A08	2007	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I081A09	2008	134-241	155-165	181-187	220-230	1-118	26-35	50-66	99-107 GAGSRYFDL	(SEQ ID NO:3118)
I081A10	2009	133-243	155-168	184-190	223-232	1-117	26-35	50-66	99-106 GGDRAFDI	(SEQ ID NO:3119)
I081B01	2010	130-236	151-161	177-183	216-225	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I081B04	2011	134-244	156-169	185-191	224-233	1-118	26-35	50-66	99-107 GNAWGAFDI	(SEQ ID NO:2211)
I081B05	2012	133-243	155-168	184-190	223-232	1-117	26-35	50-66	99-106 GGDRAFDI	(SEQ ID NO:3119)
I081B06	2013	133-240	154-164	180-186	219-229	1-117	26-35	50-66	99-106 VKRYYPDY	(SEQ ID NO:3179)
I081B07	2014	136-243	157-167	183-189	222-232	1-120	26-35	50-66	99-109 ELTGANDAFDI	(SEQ ID NO:3104)
I081B08	2015	132-239	153-163	179-185	218-228	1-116	26-35	50-66	99-105 RRYALDY	(SEQ ID NO:2920)
I081B09	2016	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I081B10	2017	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I081B11	2018	132-239	153-163	179-185	218-228	1-116	26-35	50-66	99-105 GFALYKD	(SEQ ID NO:3169)
I081C07	2019	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I081C08	2020	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I081D04	2021	135-242	156-166	182-188	221-231	1-119	26-35	50-66	99-108 EDLTGDAFDI	(SEQ ID NO:3103)
I081D06	2022	132-239	153-163	179-185	218-228	1-116	26-35	50-66	99-105 GDAYFDY	(SEQ ID NO:3147)
I081D08	2023	132-239	153-163	179-185	218-228	1-116	26-35	50-66	99-105 GDAYFDY	(SEQ ID NO:3147)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I081D09	2024	130-238	152-162	178-184	217-227	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I081D10	2025	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I081D11	2026	134-244	156-169	185-191	224-233	1-118	26-35	50-66	99-107 EQLDAFDI	(SEQ ID NO:3200)
I081D12	2027	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I081E02	2028	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I081E03	2029	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I081E05	2030	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I081E06	2031	134-241	155-165	181-187	220-230	1-118	26-35	50-66	99-107 VGYGGKGDY	(SEQ ID NO:3137)
I081E07	2032	134-241	155-165	181-187	220-230	1-118	26-35	50-66	99-107 GAGSRYFDL	(SEQ ID NO:3118)
I081E10	2033	142-249	163-173	189-195	228-238	1-126	26-35	50-66	99-115 GLAPIVDGGMTNDAFDI	(SEQ ID NO:3184)
I081F01	2034	130-239	152-164	180-186	219-228	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I081F04	2035	132-239	153-163	179-185	218-228	1-116	26-35	50-66	99-105 RLIRKAR	(SEQ ID NO:3170)
I081F05	2036	130-237	151-161	177-183	216-226	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I081F06	2037	134-244	156-169	185-191	224-233	1-118	26-35	50-66	99-107 ERGNQAFDI	(SEQ ID NO:3156)
I081F07	2038	132-239	153-163	179-185	218-228	1-116	26-35	50-66	99-105 RRYALDY	(SEQ ID NO:2920)
I081F11	2039	130-237	151-161	177-183	216-226	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I081G01	2040	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I081G04	2041	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I081G06	2042	135-245	157-170	186-192	225-234	1-119	26-35	50-66	99-108 SRSPYDAFDI	(SEQ ID NO:3097)
I081G10	2043	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I081H02	2044	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I081H03	2045	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I081H04	2046	135-242	156-166	182-188	221-231	1-119	26-35	50-66	99-108 SNWGGDAFDI	(SEQ ID NO:3202)
I081H06	2047	130-240	152-165	181-187	220-229	1-114	26-35	50-66	99-103 LAFDI	(SEQ ID NO:3174)
I081H08	2048	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I082A02	2049	139-249	161-173	189-195	228-238	1-123	26-35	50-66	99-112 PAASSRGPKDAFDI	(SEQ ID NO:3129)
I082A04	2050	130-240	152-165	181-187	220-229	1-114	26-35	50-66	99-103 LSGDS	(SEQ ID NO:3122)
I082A08	2051	134-243	156-168	184-190	223-232	1-118	26-35	50-66	99-107 EGVAAGEDY	(SEQ ID NO:3123)
I082A11	2052	130-240	152-165	181-187	220-229	1-114	26-35	50-66	99-103 FVL DY	(SEQ ID NO:2210)
I082B06	2053	131-238	154-164	180-186	219-227	1-115	26-35	50-66	99-104 GNGKDV	(SEQ ID NO:3135)
I082B09	2054	134-241	157-167	183-189	222-230	1-118	26-35	50-66	99-107 EGVAAGEDY	(SEQ ID NO:3123)
I082B12	2055	131-241	153-166	182-188	221-230	1-115	26-35	50-66	99-104 DLD PDY	(SEQ ID NO:2208)
I082C01	2056	136-243	157-167	183-189	222-232	1-120	26-35	50-66	99-109 VNDIVVVMDV	(SEQ ID NO:3143)
I082C05	2057	136-243	157-167	183-189	222-232	1-120	26-35	50-66	99-109 EKRGSRVFDI	(SEQ ID NO:3093)
I082C08	2058	137-244	158-168	184-190	223-233	1-121	26-35	50-66	99-110 LSNRNDNLRLDY	(SEQ ID NO:3106)
I082D02	2059	130-240	152-165	181-187	220-229	1-114	26-35	50-66	99-103 FVL DY	(SEQ ID NO:2210)
I082E05	2060	134-241	155-165	181-187	220-230	1-118	26-35	50-66	99-107 TWATNTFDM	(SEQ ID NO:3152)
I082E06	2061	130-240	152-165	181-187	220-229	1-114	26-35	50-66	99-103 FDL DY	(SEQ ID NO:3167)
I082E07	2062	139-246	162-172	188-194	227-235	1-123	26-35	50-66	99-112 VEWEDIVVGSADF I	(SEQ ID NO:3128)
I082F11	2063	136-243	159-169	185-191	224-232	1-120	26-35	50-66	99-109 GGD MTVT TTDY	(SEQ ID NO:3177)
I082G07	2064	136-243	159-169	185-191	224-232	1-120	26-35	50-66	99-109 ADYSNDY TMDV	(SEQ ID NO:3166)
I082G10	2065	138-249	160-173	189-195	228-238	1-118	26-35	50-66	99-107 EGVAAGEDY	(SEQ ID NO:3123)
I082G11	2066	143-250	164-174	190-196	229-239	1-127	26-35	50-66	99-116 GPIYYFGSAYEGYYFDY	(SEQ ID NO:3222)
I082H04	2067	132-238	153-163	179-185	218-227	1-116	26-35	50-65	98-105 MNADAFEI	(SEQ ID NO:3223)
I082H09	2068	139-246	160-170	186-192	225-235	1-123	26-35	50-66	99-112 PAASSRGPKDAFDI	(SEQ ID NO:3129)
I083A06	2069	137-244	159-169	185-191	224-233	1-120	26-35	50-66	99-109 DSRPTNRAHY	(SEQ ID NO:3110)

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TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I083A09	2070	138-248	160-172	188-194	227-237	1-121	26-35	50-68	101-110 LHCTGGSCGF	(SEQ ID NO:3186)
I083A11	2071	136-248	158-171	187-193	226-237	1-119	26-35	50-66	99-108 VRDSDAGFDY	(SEQ ID NO:3173)
I083B03	2072	139-247	161-171	187-193	226-236	1-121	26-35	50-66	99-110 VLVRGQYRGMDL	(SEQ ID NO:3138)
I083B05	2073	139-250	161-174	190-196	229-239	1-122	26-35	50-66	99-111 VDYTDYEMGAFDL	(SEQ ID NO:3172)
I083B06	2074	139-250	161-174	190-196	229-239	1-122	26-35	50-66	99-111 DRIAAAGGDAFDI	(SEQ ID NO:3194)
I083B10	2075	139-246	162-172	188-194	227-235	1-121	26-35	50-66	99-110 DLYKNGYALFDS	(SEQ ID NO:3197)
I083C01	2076	136-247	158-171	187-193	226-236	1-119	26-35	50-66	99-108 DEYSSLYMDV	(SEQ ID NO:3201)
I083C02	2077	136-246	158-171	187-193	226-235	1-119	26-35	50-66	99-108 FGAGRLYDDY	(SEQ ID NO:3224)
I083C07	2078	137-249	159-172	188-194	227-238	1-120	26-35	50-66	99-109 DNGGGTIGFDY	(SEQ ID NO:2195)
I083C12	2079	136-246	158-171	187-193	226-235	1-119	26-35	50-66	99-108 DQGIETANDY	(SEQ ID NO:3207)
I083D04	2080	146-256	168-181	197-203	236-245	1-129	26-35	50-66	99-118 DILPDYDFWNPEDASSLDT	(SEQ ID NO:3133)
I083D07	2081	150-262	173-188	204-210	243-251	1-132	26-35	50-66	99-121 DFQMRGVFIANPIIYNYGMDV	(SEQ ID NO:3154)
I083D08	2082	143-254	165-178	194-200	233-243	1-126	26-35	50-66	99-115 DADEGLVEAETTNWFDS	(SEQ ID NO:3126)
I083D10	2083	147-258	169-181	197-203	236-247	1-130	26-37	52-69	102-119 ATKSYDILTRMYHYHMDV	(SEQ ID NO:2748)
I083D12	2084	134-242	156-166	182-188	221-231	1-116	26-35	50-66	99-105 DRTRMDV	(SEQ ID NO:3182)
I083E02	2085	139-249	161-173	189-195	228-238	1-122	26-35	50-66	99-111 VGIAAAVDNFEY	(SEQ ID NO:2197)
I083E03	2086	136-248	158-171	187-193	226-237	1-119	26-35	50-66	99-108 DEIYNDAFDY	(SEQ ID NO:3105)
I083E04	2087	144-255	166-179	195-201	234-244	1-127	26-35	50-66	99-116 DGDISDSPINNQNAYMDI	(SEQ ID NO:3101)
I083E08	2088	140-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111 RGGTSENYSQMDV	(SEQ ID NO:3209)
I083E12	2089	135-245	157-170	186-192	225-234	1-118	26-35	50-66	99-107 DYPHNAFDI	(SEQ ID NO:3127)
I083F02	2090	146-258	168-181	197-203	236-247	1-129	26-35	50-66	99-118 DVRSDFWSSGGYFHYSGMDV	(SEQ ID NO:3131)
I083F04	2091	138-248	160-172	188-194	227-237	1-121	26-35	50-66	99-110 STLEVGAITDFDY	(SEQ ID NO:3199)
I083F06	2092	135-247	157-170	186-192	225-236	1-118	26-35	50-66	99-107 SDDWGAYHI	(SEQ ID NO:3198)
I083F08	2093	139-250	161-174	190-196	229-239	1-122	26-35	50-66	99-111 ERGGRDGYALDF	(SEQ ID NO:3148)
I083F11	2094	137-248	159-172	188-194	227-237	1-120	26-35	50-66	99-109 ELVGAPGGFDP	(SEQ ID NO:3191)
I083G04	2095	139-250	161-174	190-196	229-239	1-122	26-35	50-66	99-111 VDYTDYEMGAFDL	(SEQ ID NO:3172)
I083G05	2096	139-249	161-173	189-195	228-238	1-121	26-35	50-68	101-110 SVAGRGNFYD	(SEQ ID NO:3208)
I083G06	2097	139-250	161-174	190-196	229-239	1-122	26-35	50-66	99-111 ERGGRDGYALDF	(SEQ ID NO:3148)
I083G08	2098	142-253	164-177	193-199	232-242	1-125	26-35	50-66	99-114 EGGGDAYDVAPYYFDY	(SEQ ID NO:2204)
I083G09	2099	132-242	154-166	182-188	221-231	1-114	26-35	50-66	99-103 DPFDY	(SEQ ID NO:3134)
I083G11	2100	141-252	163-176	192-198	231-241	1-124	26-35	50-66	99-113 ALLGLPSDFSYYVDV	(SEQ ID NO:3159)
I083H04	2101	142-253	164-177	193-199	232-242	1-125	26-35	50-66	99-114 EGEGDGYNVAPYYFDY	(SEQ ID NO:3160)
I083H05	2102	135-243	157-167	183-189	222-232	1-117	26-35	50-66	99-106 TDYGGFDY	(SEQ ID NO:3092)
I083H07	2103	139-247	161-171	187-193	226-236	1-121	26-35	50-66	99-110 GGVGDSRGVFPD	(SEQ ID NO:3162)
I084A03	2104	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I084A08	2105	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I084B08	2106	135-242	156-166	182-188	221-231	1-119	26-35	50-66	99-108 ESLTGDAFDI	(SEQ ID NO:3116)
I084C02	2107	136-243	157-167	183-189	222-232	1-120	26-35	50-66	99-109 SPLHFSDAFDI	(SEQ ID NO:3120)
I084D03	2108	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I084D05	2109	133-243	155-168	184-190	223-232	1-117	26-35	50-66	99-106 EVGGAFDI	(SEQ ID NO:3157)
I084E01	2110	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I084E06	2111	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I084E10	2112	130-237	151-161	177-183	216-226	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I084E12	2113	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I084F04	2114	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)
I084F07	2115	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103 DTTDY	(SEQ ID NO:2203)

TABLE 1-continued

scFvs that Immunospecifically Bind to B Lymphocyte Stimulator										
Clone ID	scFv SEQ ID NO	AAs of VL	AAs of VL CDR1	AAs of VL CDR2	AAs of VL CDR3	AAs of VH	AAs of VH CDR1	AAs of VH CDR2	AAs of VH CDR3	VH CDR3 Sequence (SEQ ID NO)
I084F12	2116	135-245	157-170	186-192	225-234	1-119	26-35	50-66	99-108	ESLTGDAPDI (SEQ ID NO:3116)
I084G12	2117	130-240	152-164	180-186	219-229	1-114	26-35	50-66	99-103	DTTDY (SEQ ID NO:2203)
I084H02	2118	130-237	153-163	179-185	218-226	1-114	26-35	50-66	99-103	DTTDY (SEQ ID NO:2203)
I099B05	2119	146-256	168-180	196-202	235-245	1-129	26-35	50-66	99-118	GAHYDRSPSHLKSYYWYFDL (SEQ ID NO:3149)
I099G09	2120	139-249	161-173	189-195	228-238	1-122	26-35	50-66	99-111	VGIKAAAVDNFEY (SEQ ID NO:2197)
I099H01	2121	140-248	162-172	188-194	227-237	1-122	26-35	50-66	99-111	LGRNYTSSWSLDY (SEQ ID NO:3181)
I099H06	2122	139-249	161-173	189-195	228-238	1-122	26-35	50-66	99-111	VGIKAAAVDNFEY (SEQ ID NO:2197)
I099H08	2123	145-255	167-179	195-201	234-244	1-128	26-35	50-66	99-117	GGRYGYYYDGTGYVDAFDI (SEQ ID NO:3226)
I100A01	2124	137-247	159-172	188-194	227-236	1-120	26-35	50-66	99-109	DNGGGTIGFDY (SEQ ID NO:2195)
I100A10	2125	141-251	163-175	191-197	230-240	1-124	26-35	50-66	99-113	VRQQIADPPRSFFDP (SEQ ID NO:3144)
I100B03	2126	137-247	159-172	188-194	227-236	1-120	26-35	50-66	99-109	DNGGGTIGFDY (SEQ ID NO:2195)
I100B04	2127	137-247	159-172	188-194	227-236	1-120	26-35	50-66	99-109	DNGGGTIGFDY (SEQ ID NO:2195)
I100C03	2128	141-251	163-175	191-197	230-240	1-124	26-35	50-66	99-113	VRQQIADPPRSFFDP (SEQ ID NO:3144)

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SEQUENCE LISTING

The patent contains a lengthy "Sequence Listing" section. A copy of the "Sequence Listing" is available in electronic form from the USPTO web site (<http://seqdata.uspto.gov/?pageRequest=docDetail&DocID=US07605236B2>). An electronic copy of the "Sequence Listing" will also be available from the USPTO upon request and payment of the fee set forth in 37 CFR 1.19(b)(3).

What is claimed is:

1. An isolated or purified antibody that immunospecifically binds to B Lymphocyte Stimulator protein comprising:
 - (a) an amino acid sequence that is at least 85% identical to residues 1-126 of SEQ ID NO:1321; and
 - (b) an amino acid sequence that is at least 85% identical to residues 143-251 of SEQ ID NO:1049;
 wherein the B Lymphocyte Stimulator protein is selected from the group consisting of:
 - (1) a protein whose amino acid sequence consists of amino acid residues 1-285 of SEQ ID NO:3228;
 - (2) a protein whose amino acid sequence consists of amino acid residues 134-285 of SEQ ID NO:3228; and
 - (3) a trimer of the protein of (2).
2. The antibody of claim 1, wherein the antibody comprises:
 - (a) an amino acid sequence that is at least 95% identical to residues 1-126 of SEQ ID NO:1321; and
 - (b) an amino acid sequence that is at least 95% identical to residues 143-251 of SEQ ID NO:1049.
3. The antibody of claim 1, wherein the antibody comprises:
 - (a) an amino acid sequence comprising residues 1-126 of SEQ ID NO: 1321; and
 - (b) an amino acid sequence comprising residues 143-251 of SEQ ID NO:1049.
4. The antibody of claim 1, wherein the antibody is selected from the group consisting of a whole immunoglobulin molecule, a scFv a Fab fragment, a Fab' fragment, a F(ab')₂, a Fv and a disulfide linked Fv.
5. The antibody of claim 1, wherein the antibody is monoclonal.
6. The antibody of claim 1, wherein the antibody has a dissociation constant (K_D) of less than or equal to 10⁻⁹M.
7. The antibody of claim 1, wherein the antibody is labeled.
8. The antibody of claim 7, wherein the antibody is labeled with a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, or biotin.
9. The antibody of claim 1, wherein the antibody diminishes or abolishes the ability of B Lymphocyte Stimulator protein or a fragment thereof to bind to a B Lymphocyte Stimulator protein receptor.
10. The antibody of claim 1, wherein the antibody diminishes or abolishes the ability of B Lymphocyte Stimulator protein or a fragment thereof to stimulate B cell proliferation, differentiation, or survival.
11. An isolated or purified antibody that immunospecifically binds to B Lymphocyte Stimulator protein comprising:
 - (a) an amino acid sequence that is at least 90% identical to residues 1-126 of SEQ ID NO:1321; and
 - (b) an amino acid sequence that is at least 90% identical to residues 143-251 of SEQ ID NO:1049;
 wherein the B Lymphocyte Stimulator protein is selected from the group consisting of:
 - (1) a protein whose amino acid sequence consists of amino acid residues 1-285 of SEQ ID NO:3228;
 - (2) a protein whose amino acid sequence consists of amino acid residues 134-285 of SEQ ID NO:3228; and
 - (3) a trimer of the protein of (2).
12. The antibody of claim 11, wherein the antibody is selected from the group consisting of a whole immunoglobulin molecule, a scFV a Fab fragment an a Fab' fragment, a F(ab')₂, a Fv and a disulfide linked Fv.
13. The antibody of claim 11, wherein the antibody diminishes or abolishes the ability of B Lymphocyte Stimulator protein or a fragment thereof to bind to a B Lymphocyte Stimulator protein receptor, or diminishes or abolishes the ability of B Lymphocyte Stimulator protein or a fragment thereof to stimulate B cell proliferation, differentiation, or survival.
14. The antibody of claim 1, wherein the antibody further comprises a heavy chain immunoglobulin constant domain selected from the group consisting of:
 - (a) a human IgM constant domain;
 - (b) a human IgG1 constant domain;
 - (c) a human IgG2 constant domain;
 - (d) a human IgG3 constant domain;
 - (e) a human IgG4 constant domain; and
 - (f) a human IgA constant domain.
15. The antibody of claim 14, wherein the heavy chain immunoglobulin constant domain is a human IgG1 constant domain.
16. The antibody of claim 14, wherein the heavy chain immunoglobulin constant domain is a human IgG4 constant domain.
17. The antibody of claim 1, wherein the antibody further comprises a light chain immunoglobulin constant domain selected from the group consisting of:
 - (a) a human kappa constant domain; and
 - (b) a human lambda constant domain.
18. The antibody of claim 17, wherein the light chain immunoglobulin constant domain is a human kappa constant domain.
19. The antibody of claim 11, wherein the antibody further comprises a heavy chain immunoglobulin constant domain selected from the group consisting of:
 - (a) a human IgM constant domain;
 - (b) a human IgG1 constant domain;
 - (c) a human IgG2 constant domain;
 - (d) a human IgG3 constant domain;
 - (e) a human IgG4 constant domain; and
 - (f) a human IgA constant domain.

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20. The antibody of claim 19 wherein the heavy chain immunoglobulin constant domain is a human IgG1 constant domain.

21. The antibody of claim 19 wherein the heavy chain immunoglobulin constant domain is a human IgG4 constant domain.

22. The antibody of claim 11, wherein the antibody further comprises a light chain immunoglobulin constant domain selected from the group consisting of:

- (a) a human kappa constant domain; and
- (b) a human lambda constant domain.

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23. The antibody of claim 22 wherein the light chain immunoglobulin constant domain is a human kappa constant domain.

24. The antibody of claim 1, wherein the antibody further comprises a human IgG1 or IgG4 heavy chain immunoglobulin constant domain and a human kappa light chain immunoglobulin constant domain.

25. The antibody of claim 11, wherein the antibody further comprises a human IgG1 or IgG4 heavy chain immunoglobulin constant domain and a human kappa light chain immunoglobulin constant domain.

* * * * *

EXHIBIT C



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HUMAN GENOME SCIENCES INC.
INTELLECTUAL PROPERTY DEPT.
14200 SHADY GROVE ROAD
ROCKVILLE MD 20850

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In re Application of :
Rosen et al. :
Application No. 10/602,727 : ON APPLICATION FOR
Filed: June 25, 2003 : PATENT TERM ADJUSTMENT
Attorney Docket No. PF596PIN :

This is in response to the "Application For Patent Term Adjustment Under 37 CFR §1.705(b)," filed March 6, 2009. Applicants request that the initial determination of patent term adjustment under 35 U.S.C. 154(b) be corrected from four hundred (400) days to five hundred ninety-four (594) days.

The application for patent term adjustment is DISMISSED.

On December 10, 2008, the Office mailed the Determination of Patent Term Adjustment under 35 U.S.C. 154(b) in the above-identified application. The Notice stated the patent term adjustment to date is 400 days. Applicants dispute the four-day reduction for the submission of an Information Disclosure Statement (IDS) on July 11, 2006. Applicants also contend that the Notice to Comply mailed on October 13, 2006 was not a proper response under 35 USC § 154(b)(1)(A)(ii) and 37 CFR §§1.702(a)(2) & 1.703(a)(2) to applicants July 7, 2006 reply.

Applicants contend that a 4-day reduction for the submission of the supplemental reply in the form of an Information Disclosure Statement (IDS) on July 11, 2006 is not warranted. Applicants argue that a complete reply to the March 7, 2006 restriction requirement was submitted on July 7, 2006, thus the submission

of the IDS was not a supplemental paper within the meaning of 37 CFR 1.704(c)(8). Further applicants contend that the submission of the IDS could not have delayed the examiners consideration because the reply was not forwarded to the examiner until July 11, 2006.

A period of reduction of 4 days was properly entered based on 37 CFR 1.704(c)(8). The reduction is not calculated based upon the date the reply is forwarded to the examiner. 37 CFR §1.704(c)(8) provides that a period of reduction is entered for:

Circumstances that constitute a failure of the applicant to engage in reasonable efforts to conclude processing or examination of an application also include the following circumstances, which will result in the following reduction of the period of adjustment set forth in § 1.703 to the extent that the periods are not overlapping:

(8) Submission of a supplemental reply or other paper, other than a supplemental reply or other paper expressly requested by the examiner, after a reply has been filed, in which case the period of adjustment set forth in § 1.703 shall be reduced by the number of days, if any, beginning on the day after the date the initial reply was filed and ending on the date that the supplemental reply or other such paper was filed;

However, 37 CFR 1.704(d) provides that:

A paper containing only an information disclosure statement in compliance with §§ 1.97 and 1.98 will not be considered a failure to engage in reasonable efforts to conclude prosecution (processing or examination) of the application under paragraphs (c)(6), (c)(8), (c)(9), or (c)(10) of this section if it is accompanied by a statement that each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart application and that this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement. This thirty-day period is not extendable.

In this instance, after the filing of a response on July 7, 2006, on July 11, 2006, applicants filed a supplemental paper in the form of an IDS. The record supports a conclusion that the IDS was not expressly requested by the examiner. Further, the IDS did not include the §1.704(d) statement. Accordingly, the PTA was properly reduced by 4 days, the number of days beginning on the day after the date the initial reply was filed, July 8, 2006, and ending on the date that the supplemental reply or other such paper was filed, July 11, 2006. As such the 4-day reduction was warranted and will not be removed.

Applicants also contend that instead of a 64-day adjustment a 254-day adjustment is required for the Office taking in excess of four months to reply to the response to the election requirement submitted on July 7, 2006. Applicants contend that the Notice to Comply to the Sequence Listing did not constitute a reply to the response to the restriction requirement. A period of adjustment of 254 days should have been entered based on 37 CFR 1.702(a)(2).

Applicants argument has been considered, but not found persuasive that entry of an additional period for Office delay is warranted.

37 CFR 1.704(c)(7) establishes submission of a reply having an omission (37 CFR 1.135(c)) as a circumstance that constitutes a failure of an applicant to engage in reasonable efforts to conclude processing or examination of an application. Submitting a reply having an omission requires the Office to issue an action under 37 CFR 1.135(c) and await and process the applicant's reply to the action under 37 CFR 1.135(c) before the initial reply (as corrected) can be treated on its merits. In addition, 37 CFR 1.704(c)(7) provides that in such a case the period of adjustment set forth in 37 CFR 1.703 shall be reduced by the number of days, if any, beginning on the day after the date the reply having an omission was filed and ending on the date that the reply or other paper correcting the omission was filed. The reference to 37 CFR 1.135(c) is parenthetical because 37 CFR 1.704(c)(7) is not limited to Office actions under 37 CFR 1.135(c) but applies when the Office issues any action or notice indicating that a reply has an omission which must be corrected: e.g., (1) a decision on a petition under 37 CFR 1.47 dismissing the petition as lacking an item necessary to grant the petition; or (2) a notice indicating that the computer readable format sequence listing filed in reply to a Notice to Comply with

Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures (PTO-1661) does not comply with 37 CFR 1.821 et seq.

In this instance, the Office took action on October 13, 2006 in response to the response to the restriction requirement filed July 7, 2006 mailing an Office action that notified applicant that their response was considered *bonafide* but compliance with the sequence requirements was necessary. This Office communication was mailed within four months of the filing of the response, and thus, does not constitute Office delay. On January 16, 2007, applicants filed their response (which notably included an assertion that the new sequence listing is identical to the sequence listing currently on file, e.g. no omission), but also included an amendment.

It is concluded that the Office delay of 64 days was properly calculated based on the date of mailing of the Office action mailed July 19, 2007 in reply to the response to Notice to Comply filed January 16, 2007. A period of adjustment of 254 days will not be entered and the period of adjustment of 64 days will not be removed.

In view thereof, the determination of PTA at the time of the mailing of the notice of allowance remains FOUR HUNDRED (400) days.

The Office acknowledges submission of the \$200.00 fee set forth in 37 CFR 1.18(e). No additional fees are required.

Applicants are reminded that any delays by the Office pursuant to 37 CFR 1.702(a)(4) and 1.702(b) and any applicant delays under 37 CFR 1.704(c)(10) will be calculated at the time of the issuance of the patent and applicants will be notified of the revised patent term adjustment to be indicated on the patent in the Issue Notification letter that is mailed to applicants approximately three weeks prior to issuance.

The Office of Data Management has been advised of this decision. This matter is being referred to the Office of Data Management for issuance of the patent.

Telephone inquiries specific to this matter should be directed to the Petitions Attorney Charlema Grant at (571) 272-3215.

A handwritten signature in black ink, appearing to read "Nancy Johnson". The signature is fluid and cursive, with the first name "Nancy" being more prominent than the last name "Johnson".

Nancy Johnson
Senior Petitions Attorney
Office of Petitions

EXHIBIT D



UNITED STATES PATENT AND TRADEMARK OFFICE

To: ~~11/12/09~~ RSD
LVM 702107, HGS1

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OFFICE OF PETITIONS

Leydig, Voit & Mayer Ltd.
Two Prudential Plaza - Suite 4900
180 North Stetson Avenue
Chicago IL 60601-6731

In re Application of
Rueben et al.
Application No. 11/266,444
Filed: November 4, 2005
Attorney Docket No. PF523P1D1

ON APPLICATION FOR
PATENT TERM ADJUSTMENT

MIH

LEYDIG, VOIT & MAYER
RECEIVED

SEP 18 2009

PAY/TM Due Date

This is in response to the "Application For Patent Term
Adjustment Pursuant TO 37 CFR §1.705(b)," filed July 2, 2009.
Applicants request that the initial determination of patent term
adjustment under 35 U.S.C. 154(b) be corrected from sixty-six
(66) days to one hundred twenty-eight (128) days.

KAS

The request for review of the patent term adjustment is
Dismissed.

On April 2, 2009, the Office mailed the Determination of Patent
Term Adjustment under 35 U.S.C. 154(b) in the above-identified
application. The Notice stated the patent term adjustment to
date is 66 days. Applicants dispute the 49 and 13 day
reductions for the submission of the information disclosure
statements (IDS) on September 10, 2007, and August 28, 2008,
respectively.

Applicants contend that a 49-day reduction for the submission of
the supplemental reply in the form of an Information Disclosure
Statement (IDS) on September 10, 2007, is not warranted.
Applicants argue that the IDS filed on September 10, 2007 was
filed in a period after the filing of a reply to a restriction
requirement and before the mailing of a first Office action on
the merits. Thus applicants argue the submission of the IDS did
not constitute a failure of applicants to engage in reasonable
efforts to conclude examination of the application under 37 CFR
§1.704(c). Applicants also argue that the 13-day reduction for

action on August 15, 2008 did not delay prosecution because the response to the non-final Office action was not forwarded to the examiner until September 19, 2008. Thus no delay of prosecution occurred.

The Office has considered applicants' arguments but does not find them persuasive. The Office has concluded that the periods of reduction of 49 and 13 days were properly entered based on 37 CFR 1.704(c)(8). 37 CFR §1.704(c)(8) provides that a period of reduction is entered for:

Circumstances that constitute a failure of the applicant to engage in reasonable efforts to conclude processing or examination of an application also include the following circumstances, which will result in the following reduction of the period of adjustment set forth in § 1.703 to the extent that the periods are not overlapping:

(8) Submission of a supplemental reply or other paper, other than a supplemental reply or other paper expressly requested by the examiner, after a reply has been filed, in which case the period of adjustment set forth in § 1.703 shall be reduced by the number of days, if any, beginning on the day after the date the initial reply was filed and ending on the date that the supplemental reply or other such paper was filed;

In this instance, after the filing of a response on July 23, 2007, on September 10, 2007, applicants filed a supplemental paper in the form of an IDS. The record supports a conclusion that the examiner did not expressly request the filing of the IDS on September 10, 2007. Further, the IDS did not include a §1.704(d) statement. Pursuant to MPEP 2731, a written restriction requirement, a written election of species requirement, a requirement for information under 37 CFR 1.105, an action under Ex parte Quayle, 1935 Comm'r Dec. 11 (1935), and a notice of allowability (PTOL-37) are each an action issued as a result of the examination conducted pursuant to 35 U.S.C. 131. As such, each of these Office actions is a notification under 35 U.S.C. 132. Thus the submission of the IDS after the reply to the restriction requirement is deemed to be subject to a reduction pursuant to 37 CFR 1.704(c). Accordingly, the PTA was properly reduced by 49 days, the number of days beginning on the day after the date the initial reply was filed, July 24, 2007,

and ending on the date that the IDS was filed, September 10, 2007.

The reduction of 13 days for the submission of the IDS on August 28, 2008 is also warranted. The record reveals that the IDS filed on August 28, 2008, did not include a §1.704(d) statement and was not requested by the examiner. The PTA was properly reduced by 13 days, the number of days beginning on the day after the date the initial reply was filed, August 16, 2008, and ending on the date that the IDS was filed, August 28, 2008. The Office notes that the date of filing of a paper will be used in calculating any periods of reduction of patent term adjustment, not the date the paper may be forwarded to the examiner. See MPEP 2731.

In view thereof, it is concluded that the determination of patent term adjustment at the time of the mailing of the Notice of Allowance is sixty-six (66) days.

Applicants are reminded that any delays by the Office pursuant to 37 CFR 1.702(a)(4) and 1.702(b) and any applicant delays under 37 CFR 1.704(c)(10) will be calculated at the time of the issuance of the patent and applicants will be notified of the revised patent term adjustment to be indicated on the patent in the Issue Notification letter that is mailed to applicants approximately three weeks prior to issuance.

The Office of Data Management has been advised of this decision. This matter is being referred to the Office of Data Management for issuance of the patent.

Telephone inquiries specific to this matter should be directed to the Petitions Attorney Charlema Grant at (571) 272-3215.

Christina Portere Donnell for

Kery Fries
Senior Legal Advisor Attorney
Office of Patent Legal Administration